

Origins and significance of published errors in high impact factor cancer and biomedical journals

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Statement of Originality

This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work and that all assistance received in preparing this thesis and all sources have been acknowledged.

Pranujan Pathmendra

25/09/2025

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Abstract

Reliable papers are at the heart of the scientific enterprise, where researchers contribute to and use the literature to advance understanding. However, recent studies on gene research papers have identified misconduct and systematic fraud, predominantly in lower impact factor (IF) journals ($IF < 7$). Analysing 392 cell lines and 3,370 nucleotide sequence reagent identities across circular RNA (circRNA) papers in high IF journals found that 51% (60/118) papers described at least one wrongly identified sequence or problematic cell line. We also identified 22 papers that reported at least one non-verifiable (NV) claimed circRNA targeting reagent. Wrongly identified and/or NV reagents were also found in all 13 retracted circRNA papers in high-IF journals and in some earlier papers published in two high-IF journals, *Molecular Cancer* (in 2018, 2020) and *Oncogene* (in 2020). Taken together, this reflects a widespread problem, where some materials in circRNA publications in high IF journals do not align with published results.

Correcting published errors requires input from journals and publishers, who often do not respond to correction requests. PubPeer, a post-publication commentary platform, has been relied on by many to query published errors. We posted PubPeer comments about nucleotide sequence errors in 105 original papers in the journals *Molecular Cancer* ($n=86$) and *Oncogene* ($n=21$) and then examined journal responses to these comments. Three papers received published corrections at 4, 12 and 13 months after our PubPeer posts, respectively. Most comments received no author responses on PubPeer and no published corrections to address queried errors, indicating that unreliable human gene research papers are difficult to correct post-publication.

Finally, to understand the experiences of postgraduate research students and early career researchers (ECRs) regarding publication integrity, we conducted an anonymous online qualitative survey of 34 postgraduate research students and ECRs. Some participants reported negative impacts on their mental health, delays in the progress of their research, and impacts on their careers due to loss of time and resources. In contrast, others shared positive experiences, where, with sufficient education and skills, they developed new research directions and gained confidence in their skills as researchers.

Taken together, we demonstrate that unreliable literature continues to be a problem, can be difficult to correct, and meaningfully affects the research and careers of ECRs and postgraduate students.

Published material included in this Thesis and Authorship attribution statement

Figures 2.1 and 2.2, and Table 2.19 of this thesis have been published as Pathmendra, P., Park, Y., Enguita, F. J., & Byrne, J. A. (2024). Verification of nucleotide sequence reagent identities in original publications in high impact factor cancer research journals. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 397(7), 5049-5066. Results outlined in Section 2.3.1. were a re-analysis of a smaller subset of results in this paper.

Figure 1.8 of this thesis is an adaptation of Figure 1 in Byrne, J. A., Park, Y., West, R. A., Capes-Davis, A., Favier, B., Cabanac, G., & Labbé, C. (2021). The thin red line: biomedical journal responses to incorrect non-targeting nucleotide sequence reagents in human gene knockdown publications. *Scientometrics*, 126(4), 3513-3534.

Figure 1.9 of this thesis includes material published in open-access papers, Bik Elisabeth, M., Casadevall, A., & Fang Ferric, C. (2016). The Prevalence of Inappropriate Image Duplication in Biomedical Research Publications. *Mbio*, 7(3), 10.1128/mbio.00809-00816. <https://doi.org/10.1128/mbio.00809-16> and Rossner, M., & Yamada, K. M. (2004). What's in a picture? The temptation of image manipulation. *Journal of Cell Biology*, 166(1), 11-15. <https://doi.org/10.1083/jcb.200406019>

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Supervisor Statement

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Jennifer A. Byrne

25/09/2025

Support Tools and Artificial Intelligence used in this Thesis

ChatGPT-4.0-turbo was used experimentally to test how AI synthesises information from unreliable publications, as shown in Figure 5.2. I acknowledge the use of Grammarly (<https://www.grammarly.com/>) and Microsoft Word (version 16.0) Spelling and Grammar checker to improve the grammar, punctuation and clarity of my expression. Endnote 21.5 was used to manage and generate references. GraphPad PRISM 10.5.0, Microsoft PowerPoint, and Excel (version 16.0) were used to conduct analyses and create figures. NVivo 15.2.1 was used to analyse the qualitative data in Chapter 4. Beyond this, no support tools or artificial intelligence were used, and I am solely responsible for the final content.

Contributions by others

In Chapter 2, Prof. Jennifer Byrne reviewed and edited flowcharts (Figures 2.1 and 2.2) that describe targeting parameters for circRNA targeting reagents that were made by Pranujan Pathmendra. Prof. Byrne also made initial drafts of Table 2.19 based on discussions and readings with Pranujan Pathmendra, outlining future recommendations and guidelines for reporting circRNA nucleotide sequence reagents.

Ethical Review

The online survey and qualitative study (Chapter 4) were approved by the University of Sydney's Human Research Ethics Committee [Project Number: 2023/739].

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Other publications by the author during candidature

Byrne, J. A., Park, Y., Richardson, R. A., **Pathmendra, P.**, Sun, M., & Stoeger, T. (2022). Protection of the human gene research literature from contract cheating organizations known as research paper mills. *Nucleic Acids Research*, 50(21), 12058-12070.

Oste, D. J., **Pathmendra, P.**, Richardson, R. A., Johnson, G., Ao, Y., Arya, M. D., Enochs, N. R., Hussein, M., Kang, J., & Lee, A. (2024). Misspellings or “miscellings”—Non-verifiable and unknown cell lines in cancer research publications. *International Journal of Cancer*, 155(7), 1278-1289.

Pathmendra, P., Raggatt, M., Lim, M. S., Marino, J. L., & Skinner, S. R. (2023). Exposure to Pornography and Adolescent Sexual Behavior: Systematic Review. *J Med Internet Res*, 25, e43116. <https://doi.org/10.2196/43116>

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List of Abbreviations and Acronyms

AI	Artificial Intelligence
AIMOS	Association for Interdisciplinary Meta-Research and Open Science
<i>AREG</i>	Amphiregulin
<i>ASMA</i>	Actin Alpha 1, Skeletal Muscle
ATCC	American Type Culture Collection
<i>ATF3</i>	Activating Transcription Factor 3
<i>ATG10</i>	Autophagy Related 10
<i>ATG9A</i>	Autophagy Related 9A
<i>ATG9B</i>	Autophagy Related 9B
<i>B-actin</i>	Beta actin
<i>B2M</i>	Beta-2-Microglobulin (circular RNA)
<i>BACH1</i>	BTB and CNC homology 1
<i>BIM</i>	BCL2 Like 11
Blastn	Basic Local Alignment Search Tool nucleotides
BLAT	BLAST-Like Alignment Tool
<i>BMI1</i>	BMI1 Proto-Oncogene, Polycomb Ring Finger
BSJ	Back-splice junction
<i>c-myc</i>	MYC Proto-Oncogene, BHLH Transcription Factor
<i>CDC2</i>	Cyclin Dependent Kinase 1
<i>CDH10</i>	Cadherin 10
CDR1As/ciRS-7	Cerebellar Degeneration-Related Protein 1 Antisense circular RNA
ChatGPT	Chat Generative Pre-Trained Transformer
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
CHESS	Comprehensive Human Expressed SequenceS
CI	Confidence interval
Circ-[pre-fix]	Circular
circRNA	Circular RNA
COPE	Committee on Publication Ethics
COSIG	Collection of Open Science Integrity Guides

COVID-19	Coronavirus disease of 2019
CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated protein 9
<i>CTNNB1</i>	Catenin Beta 1
<i>DCC</i>	Deleted in Colorectal Carcinoma, Netrin 1 Receptor
<i>df</i>	Degrees of freedom
DNA	Deoxyribonucleic acid
DT	Document type
DVCR	Deputy Vice-Chancellor
ECRs	Early career researchers
<i>EGFR</i>	Epidermal Growth Factor Receptor
<i>ETS-1</i>	ETS proto-oncogene 1
FISH	Fluorescence In-Situ Hybridisation
<i>FOXC2</i>	Forkhead Box C2
<i>FOXO3a</i>	Forkhead Box O3
<i>G9a</i>	Euchromatic Histone Lysine Methyltransferase 2
<i>GAPDH</i>	Glyceraldehyde-3-Phosphate Dehydrogenase
<i>GAS5</i>	Growth Arrest Specific 5
<i>GFOD1</i>	Gfo/Idh/MocA-Like Oxidoreductase Domain Containing 1
<i>HNRNPL</i>	Heterogeneous Nuclear Ribonucleoprotein L
hsa_circ	Human circular RNA
<i>HuR</i>	ELAV Like RNA Binding Protein 1
ICC/ESOMAR	International Chamber of Commerce/European Society for Opinion and Marketing Research
ID	Identifier
IF	Impact factor
ISH	In-Situ Hybridisation
<i>Itga6</i>	Integrin Subunit Alpha 6
<i>Kcnq1ot1</i>	KCNQ1 Opposite Strand/Antisense Transcript 1
let-7d	MicroRNA Let-7d
<i>LINC/Inc</i>	Long non-coding
<i>IncGCMA</i>	Gastric Cancer metastasis-associated IncRNA
IncRNA	Long non-coding RNA

MC	<i>Molecular Cancer</i>
MDPI	Multidisciplinary Digital Publishing Institute
MIQE	Minimum Information for Publication of Quantitative Real-Time PCR Experiments
miR [as prefix] or miRNA	microRNA
<i>MMP3</i>	Matrix Metalloproteinase 3
mRNA	Messenger RNA
MRPS35	Mitochondrial Ribosomal Protein S35
MS	Microsoft
ncRNA	Non-coding RNA
<i>NFAT1</i>	Nuclear Factor of Activated T Cells 2
NHANES	National Health and Nutrition Examination Survey
NR	Not reported
NV	Non-verifiable
NZ	New Zealand
ONC	<i>Oncogene</i>
P1, P2...	Participant 1, Participant 2...
<i>P27</i>	Cyclin Dependent Kinase Inhibitor 1B
PCR	Polymerase chain reaction
PCR-ChIP	Polymerase Chain Reaction – Chromatin immunoprecipitation
PhD	Doctor of Philosophy
piRNA	Piwi-interacting RNA
PMID	PubMed Identifier
<i>PRAS40</i>	AKT1 Substrate 1
<i>PRC1</i>	Protein Regulator of Cytokinesis 1
PRIMeR	Publication and Research Integrity in Medical Research
PT	Publication title [journal name on Web of Science]
<i>PTBP1</i>	Polypyrimidine Tract Binding Protein 1
<i>PTK2</i>	Protein Tyrosine Kinase 2
PVCRs	Pro Vice-Chancellor
PY	Publication year

R&D	Research and development
<i>Raptor</i>	Regulatory Associated Protein of MTOR Complex 1
RNA	Ribonucleic acid
RT-PCR	Real time – polymerase chain reaction
shRNA	Short hairpin RNA
siRNA	Small interfering RNA
SMARCA5	SNF2 Related Chromatin Remodelling ATPase 5
<i>SNAI2</i>	Snail Family Transcriptional Repressor 2
<i>SOX1</i>	SRY-Box Transcription Factor 1
<i>SOX2</i>	SRY-Box Transcription Factor 2
STM	Science, Technical and Medical publishers
<i>TIGAR</i>	TP53 Induced Glycolysis Regulatory Phosphatase
UK	United Kingdom
USA/US	United States of America
<i>WNT1</i>	Wnt Family Member 1

Chapter 1: Introduction

1.1 Publication integrity

1.1.1 Research functions on trust and truth

One of the earliest records of science practised by society was astronomy, where the Ancient Egyptians, driven by their curiosity, looked to the stars and accurately transcribed mathematical explanations of theorems (Parker, 1974) that are still studied and interpreted today. Insights then turned inward, and during the Hellenistic age, biology and medicine proliferated as research disciplines (Charitos et al., 2022). Since Aristotle's biological studies of lagoons, many individuals have come together over time, building on the published record and developing paradigms that have guided science at different points in time. As Kuhn (2014) postulated, science functions according to two main phases. During the "normal science" phase, researchers expand the existing framework. During the "revolution" phase, anomalous observations that contradict the existing paradigm catalyse a "crisis in science". Researchers then attempt to build a new paradigm that resolves the anomaly (Figure 1.1). Science is, therefore, a communal and collaborative enterprise that has undergone massive ideological and paradigmatic changes. Crucial to the propagation of science is the accuracy of records clearly outlining these empirical thoughts and methods for future generations of researchers who can trust that the preceding work was conducted accurately and honestly.

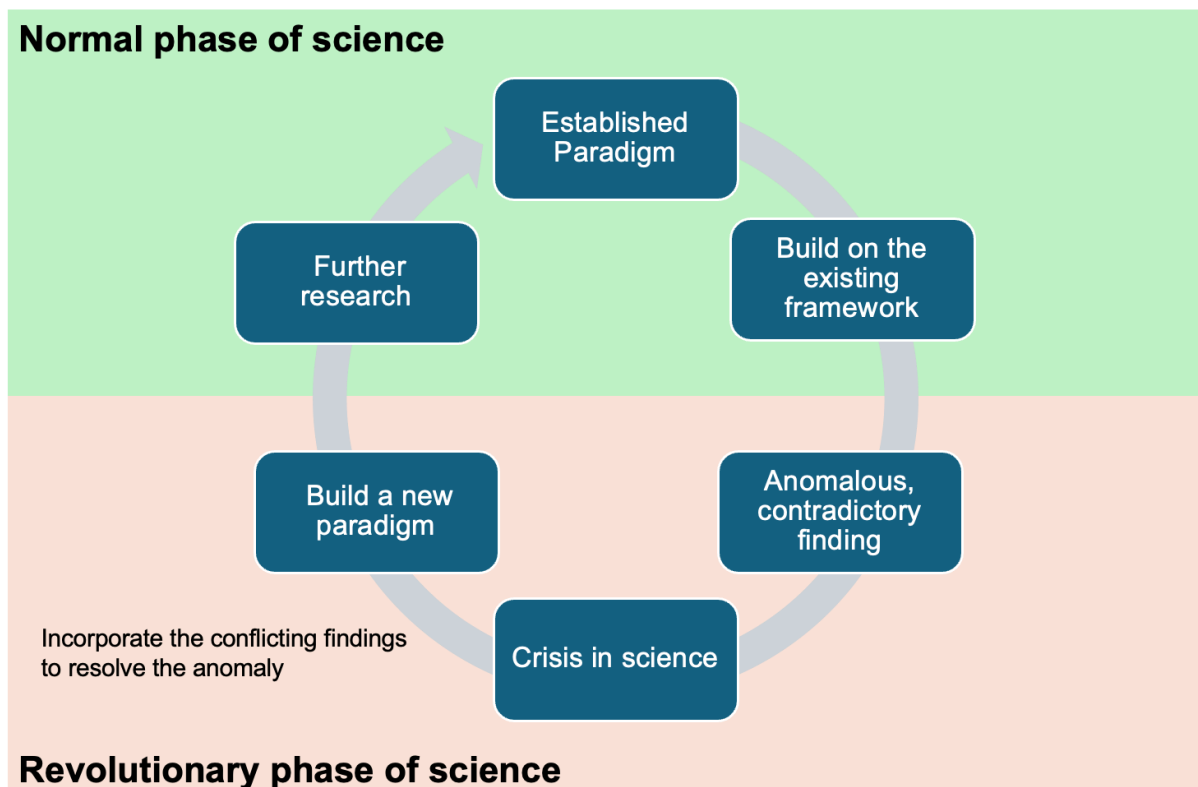


Figure 1.1. A visualisation of how science functions according to normative and revolutionary phases, as postulated by Kuhn (2014).

1.1.2 Defining publication integrity

Publication integrity is defined as the reliability of the methods, data, analyses, results and conclusions of a publication (Bolland et al., 2025) and is central to the propagation of science. Queries of publication integrity can originate in three contexts: differences of opinion between researchers, human error and as a sign of research misconduct (Figure 1.2) (Resnik & Stewart Jr, 2012).

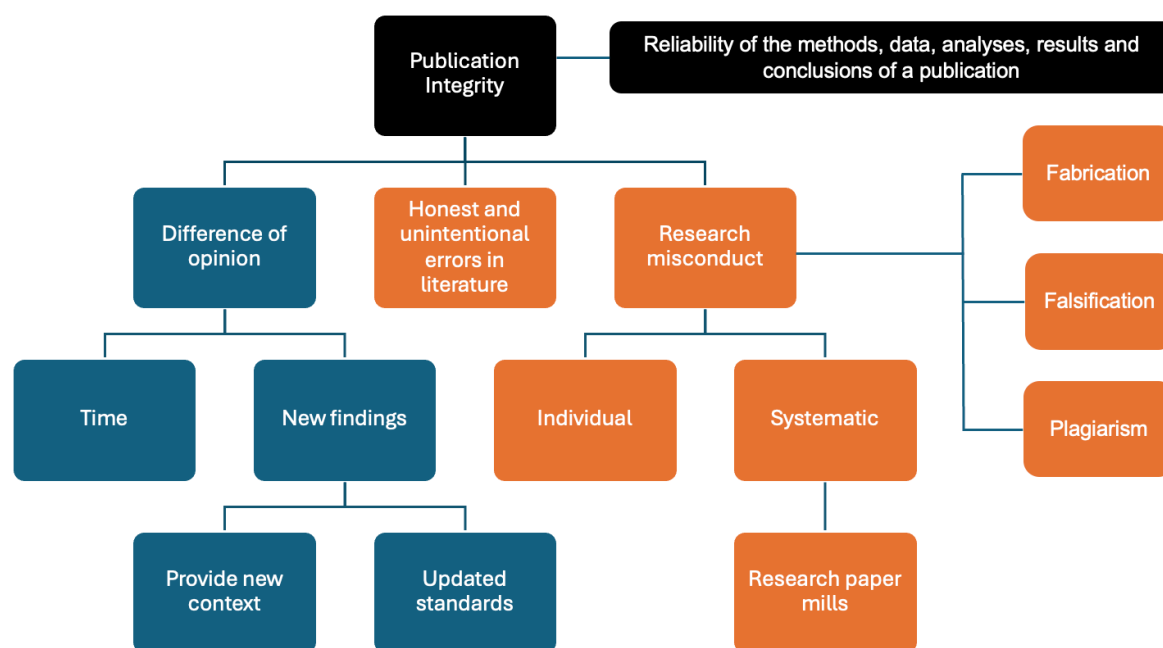


Figure 1.2. An organisational chart summarising the causes of queries on publication integrity. Blue boxes represent differences in opinion, while orange boxes represent queries associated with published errors (inspired by Resnik & Stewart Jr, 2012)

1.1.3 Scientific disagreements and differences of opinion

Differences of opinion among researchers can lead to reinterpretation of existing publications as new knowledge is discovered, where the integrity of the original publication can be potentially questioned (Figure 1.2). One example is the controversy surrounding the integrity of Gregor Mendel's work on inheritance, upon which much of modern genomics and genetics is founded. Mendel proposed a counterthought to the then-dominant paradigm of blended inheritance, proposing that distinct traits are passed separately from parent to offspring, rather than as a mix of parental traits, based on his experiments with garden peas (Mendel, 1901). Mendel's work was sidelined for decades, as this was published in a relatively obscure journal, and widely

unaccepted by fellow biologists. His use of statistical methods and mathematical logic was unfamiliar to many in the community (Berry & Browne, 2022).

Mendel's work was rediscovered decades later and adopted into the mainstream scientific paradigm. Hugo de Vries and his colleagues reproduced Mendel's findings and developed the chromosomal theory of inheritance, which contextualised Mendel's findings (Kottler, 1979). However, Mendel's observed data aligned remarkably with his predicted ratios, and thus, secondary analyses raised accusations that Mendel had excluded data, shown some form of bias, and potentially falsified his data (Franklin et al., 2008). A more recent examination verified Mendel's general findings as accurate but acknowledged the possibility of unconscious bias and proposed that Mendel's paper was simplified for biologists who were unfamiliar with the mathematical nature of his methodology (Weeden, 2016). This controversy, along with numerous publications re-assessing Mendel's original work, emphasises how queries of publication integrity can arise from differences and disagreements between scientists that emerge over time.

1.1.4 Honest and unintentional error

An alternative source of poor publication integrity is honest error, typically resulting from data mismanagement, methodological flaws, and accidental or unintended errors during manuscript preparation (Figure 1.2) (Resnik & Stewart Jr., 2012). We rely on science being self-correcting to address these mistakes and ensure the literature remains reliable (Merton, 1942). We therefore rely on researchers to participate in peer

review, whether pre- or post-publication, to ensure that our colleagues' work is accurate and reliable (Knoepfler, 2015; Tennant, 2018). Simultaneously, we also expect researchers to proactively self-correct or retract their publications when necessary to address questions of integrity that can stem from unintended errors (Hosseini et al., 2018). Although self-acknowledgement of errors is often perceived as damaging one's reputation, evidence suggests that such practices can have a positive impact on reputation and how one's work is cited (Hosseini et al., 2018; Lu et al., 2013).

1.1.5 Research misconduct

Research misconduct can be broadly defined as practices of fabrication, falsification, and plagiarism in proposing, performing, reviewing, and reporting findings (Gross, 2016; Office of Research Integrity, n.d.) (Figure 1.2). In the context of publication integrity, fabrication is the invention of data or results, falsification is the manipulation of research methods and results to suit pre-defined conclusions or reporting them unreliably, and plagiarism is the appropriation of existing work without proper citation (Bolland et al., 2025; Office of Research Integrity, n.d.). Hence, queries of publication integrity can reflect research misconduct (Figure 1.2), as evidenced by the increasing prominence of misconduct as the cited reason in retraction notices in the past decade (Chen et al., 2018; Freijedo-Farinas et al., 2024; Hwang et al., 2023) compared to earlier years where honest error was the prominent reason for retraction (Gaudino et al., 2021; Wager & Williams, 2011).

Although misconduct has been a part of science since its inception, it is in the 21st century that science has been undergoing a 'crisis in confidence', 'reproducibility crisis' or 'replication crisis' (Fanelli, 2018). Ioannidis (2005) proposed that there was a greater statistical probability for most published research findings to be false than true, beginning a crisis in confidence where the discipline of 'meta-research' or 'research on research' proliferated. In line with Kuhn's views on the periodic nature of science (Kuhn, 2014), it can be argued that the current revolution or crisis in science that researchers need to address is the concept of trust and whether research is reliable.

The replication crisis first materialised in psychology, where the then esteemed researcher Diederik Stapel confessed to falsification and fabrication upon being exposed by his students, resulting in the retraction of 58 of his publications by 2015 (Gross, 2016). This led to massive public attention to integrity, and a knock-on effect where retrospective investigations of publication integrity and reproducibility, as well as replication projects in social psychology, yielded worrying extents of irreproducibility and unreliable publications (Open Science Collaboration, 2015). This crisis eventually spread to other disciplines, including medicine, economics, political science, and even the natural sciences such as chemistry and biology (Forbes et al., 2023). One of the most recognisable cases in medicine was that of Eric Poehlman, who became the first US scientist jailed for scientific fraud. He published 10 papers with fabricated patient data and defrauded the US government of US\$2.9 million in research grants (Dalton, 2005; Gross, 2016). Hence, the combined attention to misconduct in high-profile cases, associated with waste in research funding, underpins a rising focus on examining publication integrity to identify and assess research misconduct. As evidence, 67% retractions of publications by authors affiliated with European

institutions from 2000 to 2021 cited some form of research misconduct (Freijedo-Farinas et al., 2024).

1.1.6 Commercialisation of the research enterprise and its impact on culture

The commercialisation of science, where scientific knowledge is translated into marketable products and services, has catalysed an explosion of knowledge and, consequently, numerous advancements that have bettered society (Mirowski, 2011). Simultaneously, this commercialisation has also contributed to hypercompetitive research environments (Fochler et al., 2016; Kamerlin, 2015) where publications are seen increasingly as the currency of academic career progression (Anderson et al., 2007; Fogarty, 2009; Yi et al., 2019) as opposed to their original purpose of disseminating scientific truth. The concept of “publish or perish” originates from systemic pressures where unreasonable publication quotas are imposed on researchers as a criterion for career progression (Aulakh, 2016), particularly on doctoral students (Wu, 2025) or early career researchers (ECRs) (Fien et al., 2022; Receveur et al., 2024). The phenomenon is not unique to researchers but also extends to adjacent careers. For example, physicians (Hong et al., 2013) and pre-medical students (Kuschner, 2000) in China describe being expected to meet publication quotas, in addition to their clinical work, to advance their careers.

Consequently, researchers in pressurised systems are not only demoralised and “burned out” (Tijndik et al, 2013; Haven et al., 2019b), but some can engage in

misconduct to short-cut research processes and publish to achieve their career expectations (Al-Adawi et al., 2016; Boulbes et al., 2019; de Vries et al., 2006; Herndon, 2016; Krstić, 2015; Ljubenković et al., 2021; Mabou-Tagne et al., 2020; Wu, 2025). These negative and demoralising experiences result in a perversion of the value of academic publications (Christian et al., 2021), where they are increasingly valued for their quantity instead of quality.

1.1.7 Research paper mills

Misconduct can also operate at a systemic level, where poor publication integrity can be a sign of publications originating from contract cheating organisations, such as research paper mills (Figures 1.2, 1.3) (Byrne & Christopher, 2020; Byrne et al., 2022). One of the earliest known third-party 'bad actors' is essay mills that offer complete essays and assessments to students in exchange for payment (Khan, 2022; Stavisky et al., 1973).

The term "paper mill" was initially used as a homonym for student "essay mills" (Stavisky et al., 1973). However, recently, the term "paper mill" has been used to describe contract cheating organisations that offer ready-made manuscripts in exchange for payment (Byrne, 2019; Byrne & Christopher, 2020; Byrne et al., 2022; Else & Van Noorden, 2021; Hvistendahl, 2013; Parker et al., 2024). Such fraudulent organisations are alleged to operate in various countries (Abalkina et al., 2025; Parker et al., 2024), with numerous investigations pointing to their presence in China, Iran, India, and Russia (Abalkina, 2023; Candal-Pedreira et al., 2022; Hvistendahl, 2013).

Candal-Pedreira et al. (2022) identified biomedical researchers, notably medical professionals, as the main clients of paper mills. Springer Nature's investigations identified a broad paper mill clientele, including doctoral students, doctors, politicians and predominantly senior researchers, who were driven by a need to attain publication quotas for successful progression in their careers (Kleiner, 2024).

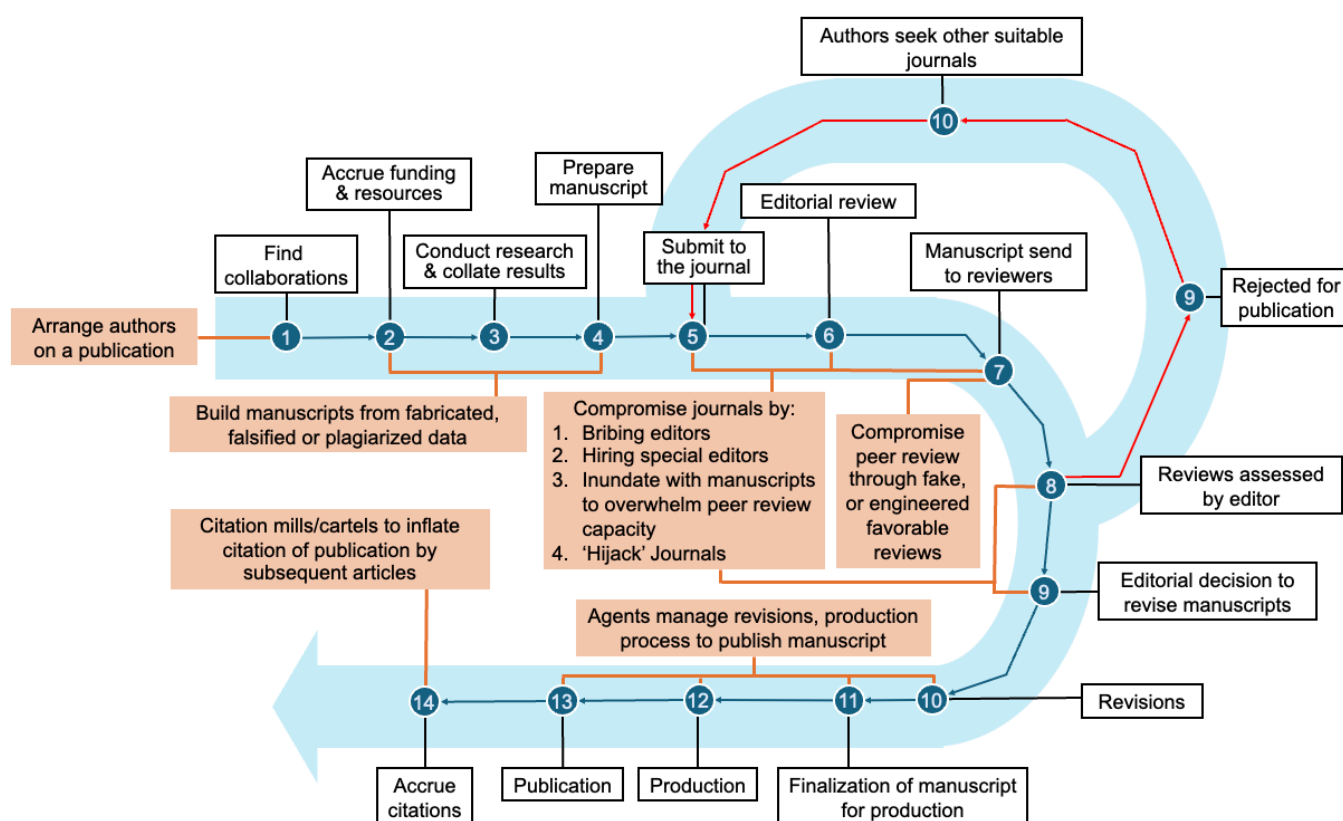


Figure 1.3. Overview of how paper mills infiltrate research and publication processes. Blue lines and black text boxes represent the standard process, where the red line represents manuscript rejection. Orange boxes represent paper mill activity.

Whilst the structure and operations of paper mills remain unknown, investigations reveal that paper mills may not only wholesale manuscripts but also facilitate other functions within the publishing ecosystem (Figure 1.3). Research paper mills may

suggest a special issue for their products, where an editor either intentionally (if bribed) or unintentionally relies on compromised peer-reviewers for favourable reviews and subsequent publication of fraudulent manuscripts (Parker et al., 2024). There have been numerous retractions of papers citing paper mill activity (Candal-Pedreira et al., 2022). For example, a subsidiary of Wiley, Hindawi, retracted over 8,000 papers in 2023 due to compromised peer review, where research paper mills had targeted special collections with editors who facilitated the publication of these fraudulent manuscripts (Van Noorden, 2023). Case studies have also demonstrated networks of editors and authors who may cooperate to publish manuscripts (Richardson et al. 2025). Alternatively, research paper mills might be affiliated with “hijacked journals” that are essentially a copy of legitimate journals (Abalkina, 2021; Parker et al., 2024). Research paper mills could also potentially engage with citation mills/cartels (Ibrahim et al., 2025) or review mills that cite paper mill papers (Oviedo-Garcia, 2024). In summary, paper mills add falsified and fake information to the scientific record by exploiting vulnerable researchers who may leverage these organisations to meet publication quotas for career progression, at the expense of publication integrity.

1.1.8 Researcher responsibilities regarding publication integrity

The research literature serves as a workplace for many researchers (Byrne & Barnett, 2024), where they assume various roles as contributors, stewards, and consumers (Figure 1.4). Researchers contribute to the literature by accruing grants, resources, and collaborations to pioneer active scientific research (Lepori et al., 2023). Researchers are expected to ensure that their publications are accurate and thereby

act as stewards of the literature, maintaining publication integrity, reliability, and trust (Parker et al., 2022). Researchers are also consumers of publications, where a single researcher reads approximately 20-26 publications per month, using information in these papers to gather new knowledge, discover new methods, and inform future research (Tenopir et al., 2019). As such, reading unreliable and irreproducible publications could result in waste of funds and resources (Freedman et al., 2015) and further misdirect future research (Byrne et al., 2019, Byrne et al., 2022).

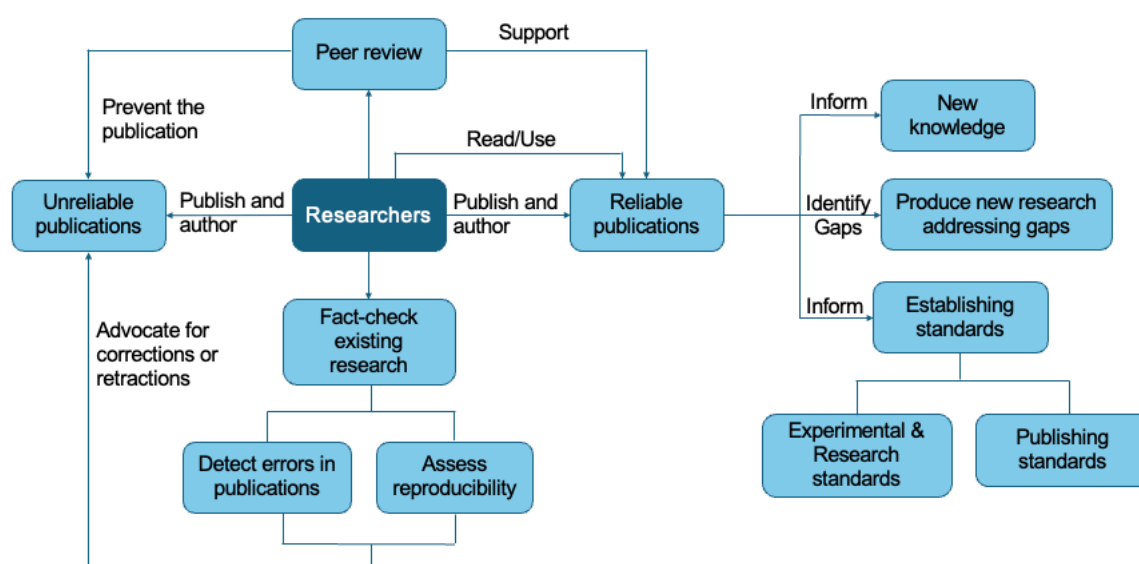


Figure 1.4. Diagram summarising the actions taken by researchers as contributors, stewards and consumers of reliable and unreliable publications.

1.1.9 Are ECRs and students more vulnerable to poor publication integrity?

The notion that researchers are impacted by poor publication integrity was discussed by Schmidt (2021), who reported anecdotally that a principal investigator stated that

at an earlier stage of their career, they were easily convinced that it was their fault if they could not reproduce a finding. This was corroborated by Lubega et al. (2023), where 82% biomedical doctoral students believed that a failure to reproduce published results was due to an error on their part. Researchers recalled feelings of self-doubt, frustration and depression through experiences with unreliable publications (Lubega et al., 2023; Schmidt, 2021).

Schmidt (2021) described another principal investigator losing a PhD student due to the pursuit of irreproducible research results. A survey of PhD students across three Scandinavian universities (Hofmann et al., 2020) found that 10% respondents expressed awareness that research misconduct was common in their disciplines. Surveys have also consistently reported that some ECRs and postgraduate students are both aware of and sometimes engage in research misconduct and other behaviours that damage publication integrity (Hofmann et al., 2020; Krstić, 2015; Tijdink et al., 2014). Several studies suggest that ECRs may place more emphasis on journal metrics such as the journal impact factor (IF) and citations as proxies for research quality (Nicholas et al., 2017; Tenopir et al., 2016), despite such metrics being easily inflated and manipulated (Shanta et al., 2013; Siler & Larivière, 2022). Hence, given their exposure and vulnerability to poor publication integrity, we need to better understand the awareness, experiences, and impacts of unreliable research from the perspectives of postgraduate research students and ECRs.

1.2 Gene Research & Publication Integrity

1.2.1 Bibliometrics

Since first sequencing the human genome (Lander et al., 2001), biomedical research has increasingly focused on characterising human gene functions and roles in disease (Byrne et al., 2022). Consequently, human genetics and genomic research have accrued public and private funding (Coles & Mensah, 2017; Tripp & Grueber, 2021). According to the Web of Science, there are 2,855,612 documents categorised as original research papers in Biochemistry and Molecular Biology or Genetics & Heredity published from 1900 to 2024, where 60% papers were published between 2000 and 2024 (Figure 1.5).

Over the past 40 years, researchers have annotated specific genes as protein-coding based on the known or predicted function of the encoded protein, where, according to GENCODE (Release 41), there are approximately 19,000 protein-coding genes (Amaral et al., 2023). Whilst initially disregarded as “junk” DNA (Boland, 2017), the development of high-throughput RNA sequencing and other technological advancements has led to the discovery of genes that do not encode proteins (Mattick et al., 2023). There is a lack of consensus on the total number of noncoding genes, ranging from approximately 20,000, as reported in the CHES database (Pertea et al., 2018), to 100,000 in the LncBook database (Ma et al., 2018). Several non-coding RNAs (ncRNAs) have been described as exerting regulatory functions across a broad range of cell types, with causal links to brain evolution as well as immune-mediated

roles in human disease (Poller et al., 2023). As such, there are many protein-coding and non-coding genes available for study and functional characterisation.

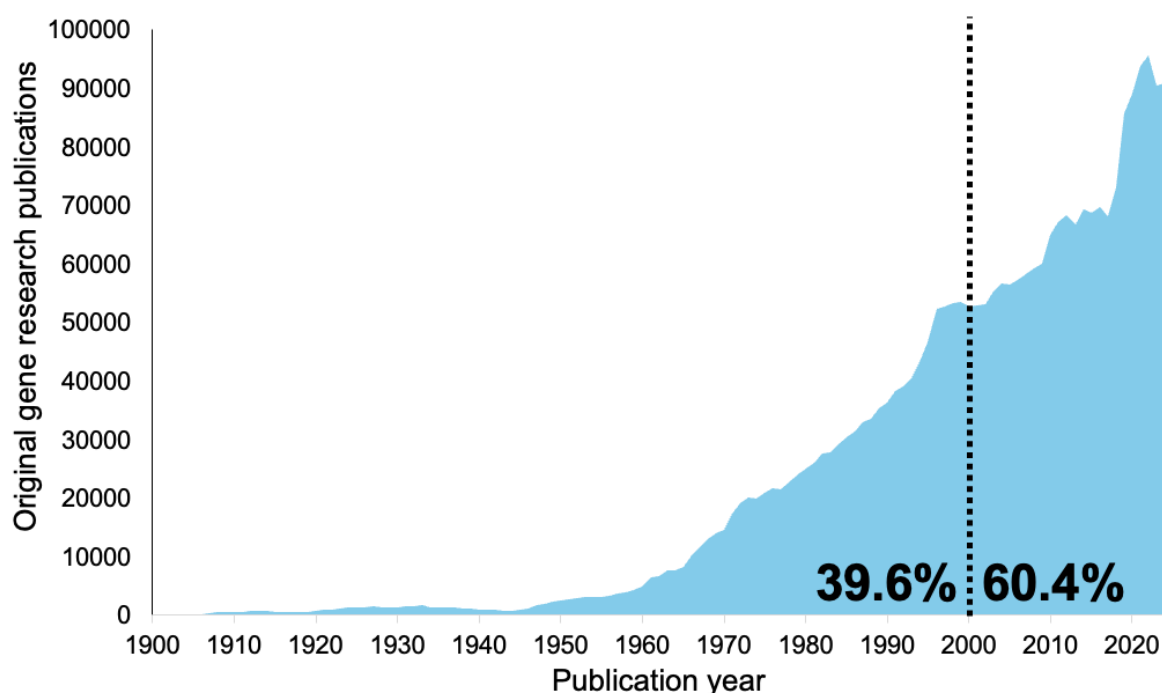


Figure 1.5. Number of gene research publications (Y-axis) published per year (X-axis) according to Web of Science. A search was conducted on the Web of Science Core Collections, Categories = “Genetics and Hereditary” OR “Biochemistry and Molecular Biology, Article Type = “Article”, Publication Year = NOT ‘2025’, to identify gene research publications. The black dotted line represents 2000, and percentages of publications from 1900-1999, and 2000-2024 are shown on either side. The Web of Science search was conducted on 30th April 2024.

1.2.2 Understudied genes

A fundamental component of building accurate biomarkers of disease and therapeutic targets is the characterisation of target genes and their biological significance (Byrne et al., 2019). However, despite the diversity of candidate genes available for functional

assays and further biological characterisation, some genes tend to be preferentially studied (Stoeger et al. 2018). This can reflect biases in favour of positive results, researcher familiarity with well-studied genes and an overall unwillingness to focus on understudied genes, given perceived implications on career prospects (Byrne et al, 2019; Richardson et al., 2024; Sinha et al., 2018; Stoeger et al., 2018). Genes can remain understudied due to lack of reagents and absence of tested protocols to confidently conduct experiments (Byrne et al., 2022; César-Razquin et al., 2015; Richardson et al., 2024). Consequently, many proteins are annotated based on sequence conservation with no or limited studies characterising their specific biological, biochemical, genetic, or cellular functions (Reynolds et al., 2021). As such, published gene research reflects in-depth knowledge of relatively few protein-coding genes and fewer ncRNAs (Byrne et al., 2022; Sinha et al., 2018), despite the number of human genes available for study (Amaral et al., 2023).

1.2.3 Molecular gene research

Gene research often begins with molecular characterisation based on a gene's predicted role within a particular disease or biological function. These experiments can include “knock out” studies where the gene is disabled or silenced through RNA interference, using small interfering (siRNA) or short-hairpin (shRNA) RNAs (Wu et al., 2022), or CRISPR/Cas9 (Poe et al., 2018). Genes can also be characterised through predictive computational methods, either through *ab initio* methods, homology-based methods, or combined methods that employ the two approaches. *Ab initio* approaches include statistical models to identify promoters, coding or non-coding regions, intron-exon junctions, and other splicing features to predict the gene's functionality (Ejigu &

Jung, 2020). In contrast, homology-based methods involve aligning the sequence to well-characterised genes and their genomic features to detect similarities that can be used to functionally annotate the studied gene and predict its potential function (Alberts et al., 2002; Ejigu & Jung, 2020; Modrek & Lee, 2002). Given the conserved sequences of ncRNAs across species, researchers tend to use computational methods to identify and characterise ncRNA genes (Abbas et al., 2016; Xu et al., 2022).

Computational predictions of gene function rely on knowledge bases of well-characterised genes. As such, accurate information on gene function is fundamental to predictive classifications of understudied and unknown genes, as well as enabling follow-up research, where researchers often build on functionally annotated genes to develop biomarkers and therapeutic targets (Byrne et al., 2019). However, it has been well-documented that errors persist in the gene literature, both across protein-coding genes (Park et al., 2022) and ncRNA gene research (Lou et al., 2024), implying that some information used by molecular researchers is unreliable.

1.2.4 The exponential growth of ncRNA research

In the context of cancer and gene research, much attention has been focused on regulatory ncRNAs, including microRNA (miRNA), piwi-interacting RNA (piRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA) (Loganathan & Doss, 2023), as potential therapeutic targets and biomarkers of disease. Bibliometric studies of miRNA research in cancer reveal an exponential growth in research papers from 2012

to 2019, compared to prior years (Shaw et al., 2022). Similarly, circRNA research has experienced a sharp increase, from 35 publications in 2015 to 1,812 papers in 2022 (Yehui et al., 2024). These sharp increases in recent publication numbers have been primarily attributed to authors in China (Shaw et al., 2022; Yehui et al., 2024).

At the same time, concerns have been raised about the integrity of ncRNA research. From 2000 to 2023, 1.8% of ncRNA papers have been retracted, and 5.7% have PubPeer queries challenging their integrity (Lou et al., 2024). Other studies have described methodological errors in miRNA and/or circRNA research publications, which were predominantly authored by teams from China affiliated with hospitals (Park et al., 2022; Pathmendra et al., 2024). Given that China has become the largest producer of research publications globally (Tollefson, 2018), it is possible that errors in papers by authors from China are reflective of broader trends. However, it is also possible that ncRNA research is vulnerable to misconduct and potentially targeted by research paper mills (Byrne et al., 2022).

1.2.5 Susceptibility of gene research to fraud

Gene research has been proposed to be susceptible to systematic research fraud, such as the production of fraudulent gene research studies by paper mills, for several reasons (Byrne et al., 2019). Gene research can be studied through common experimental pathways, or studies can be created by connecting a gene to a specific cancer type, hallmark or phenotype using cancer cell lines or samples (Byrne et al., 2019; Byrne & Labbé, 2017) (Figure 1.6). This patterning creates numerous

publication possibilities that can be further extended by the addition of other genes or regulatory elements, such as ncRNAs (Figure 1.6) (Park et al., 2022; Pathmendra et al., 2024). This results in a diversity of potential research avenues that fraudulent actors can exploit. Furthermore, many reagents such as nucleotide sequences and cell lines can be sourced from different companies and reused across many studies (Bairoch, 2018; Byrne et al., 2022; Geraghty et al., 2014), meaning that methodological details can be easily built from widely available reference materials.

The **circular RNA 001971/miR-29c-3p** axis modulates **colorectal cancer** growth, metastasis, and angiogenesis through **VEGFA**

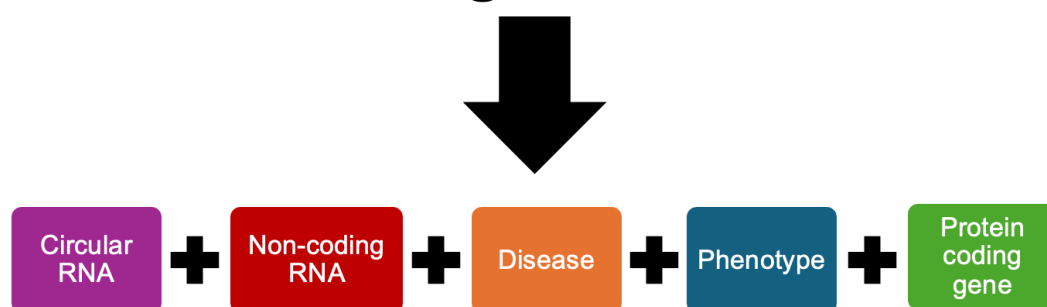


Figure 1.6. Summary of how gene research can be templated, using PMID 32430042 as an example, a retracted circRNA publication in *Journal of Experimental and Clinical Cancer Research* (2022 IF = 11.3) describing wrongly identified nucleotide sequence reagents. The title shows a circRNA (purple), ncRNA (red), protein-coding gene (green), phenotypes (blue), and a disease (orange). These elements can be varied and connected (see flowchart below) to potentially create many templated manuscripts.

As many human genes are understudied (Stoeger et al., 2018), research paper mills can incorporate understudied genes, such as ncRNAs, into their manuscripts (Figure 1.6) to add novelty. This approach could also challenge peer review by introducing unfamiliar content, thereby increasing the likelihood of publication (Byrne et al., 2019). Furthermore, gene research is adjacent to the disciplinary expertise of physicians who have frequently been discussed in the context of the ‘publish or perish’ narrative as possible clients of research paper mills (Hong et al., 2013; Parker et al., 2024). This was echoed in Park et al (2022), where the large number of gene research papers describing wrongly identified reagents were authored by teams predominantly affiliated with hospitals, reflecting the possibility that some physicians are turning to research paper mills that produce unreliable papers. Collectively, this underpins a concerning possibility that gene research is vulnerable to research fraud.

1.2.6 Limited replicability of human gene research

The clinical translation of gene research into biomarkers or therapeutic targets is often inefficient (Byrne et al., 2019; Finan et al., 2017). The Cancer Biology Reproducibility Project aimed to study whether effects reported in papers studying gene function in cancer could be independently replicated (Errington et al., 2021a, 2021b). In this project, across the 193 experiments in 53 papers, none of the papers provided sufficient detail to repeat the experiments, and only 4 papers had publicly accessible data required to independently compute effect sizes and power analyses. The authors reported that they were unable to obtain additional data for 68% experiments (Errington et al., 2021a). This highlighted that many published experiments could not be reproduced without additional information, in contrast to the reasonable expectation

that publications are sufficiently detailed for results to be replicated. The authors also repeated 50 experiments from 23 papers, analysing the replicability of 158 effects where the median effect size upon replication was generally 85% smaller than in the original experiments, with an overall replication rate of 46% (Errington et al., 2021b). As established in this project, one of the main roadblocks to reproducing published experiments was the lack of sufficient detail in materials and methods (Errington et al., 2021a). This concern over methodological integrity is echoed in studies of the integrity of human gene research papers, where key reagents have been found to be wrongly identified (Byrne et al. 2019; Byrne and Labbé, 2017; Byrne et al., 2022; Labbé et al., 2019; Park et al., 2022; Pathmendra et al., 2024).

1.2.7 Wrongly identified reagents in gene research papers

1.2.7.1 Cell lines

Cell lines are cultured cells from specific donors that proliferate indefinitely and are considered immortal (Masters, 2002). Cell lines are frequently used as models in gene research, particularly in the context of cancer research (Wilding & Bodmer, 2014). The first immortalised cell line was the HeLa cell line, derived from a cervical carcinoma patient (Masters, 2002). However, HeLa cells have contributed to a common problem in cell culture (Figure 1.7), where cross-contamination can result in contaminated cell lines no longer corresponding to the original donor (Lucey et al., 2009; Masters, 2002).

One of the most common contamination sources is the HeLa cell line, where cell lines of other cancer types can be easily transformed into hybrids or complete models that

resemble HeLa cells (Figure 1.7) (Lucey et al., 2009). Use of contaminated cell lines can thus lead to invalid data, where researchers claim to study genes in a particular disease context, yet the cell line is invalid due to cross-contamination and subsequent misidentification (Capes-Davis et al., 2010). Despite being first recognised in the late 1960s, the use of contaminated and misidentified cell lines remains common in research (Capes-Davis et al., 2010). This contamination of the literature is not decreasing, and it was estimated that papers employing HeLa contaminated cell lines have been cited by approximately 500,000 other papers (Horbach & Halfman, 2017). Recently, Oste et al. (2024) described claimed human cell lines that could not be sourced from claimed repositories and yet were used as independent cell lines. The use of misidentified and non-verifiable (NV) cell lines is a serious issue affecting the integrity of some human gene research and is likely to contribute to the problem of irreproducibility.

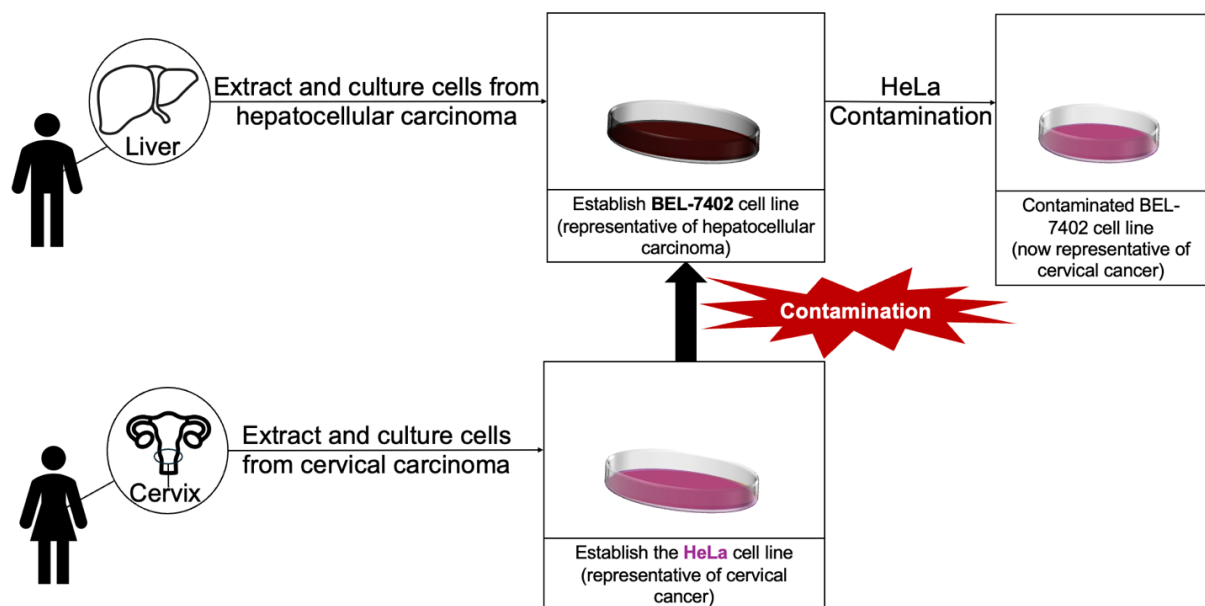


Figure 1.7. Summary of HeLa contamination of the BEL-7402 cell line, where black reflects liver cells and purple reflects cervical carcinoma cells.

1.2.7.2 Nucleotide sequence reagents

Nucleotide sequence reagents, such as PCR primers and other oligonucleotide probes, are used to target specific genes and assess them in experiments (Byrne et al., 2019; Byrne & Labbé, 2017). These short sequences are like barcodes in that their identities are not visually intuitive, and in-text descriptors are therefore crucial to decode their identities (Bustin et al., 2009; Byrne et al., 2019; Labbé et al., 2019; Taxman et al., 2010; Taylor & Mrjusich, 2014). Nucleotide sequence reagents are verifiable as their claimed identities can be independently checked using algorithms such as Blastn (Altschul et al., 1990) and BLAT (Kent, 2002).

Byrne and Labbé (2017) described mismatches between the claimed and verified identities of nucleotide sequence reagents in papers assessing the functions of single human genes in cancer cell lines (Figure 1.8). The authors went on to describe three error types: (i) nucleotide sequences claimed to target a human gene but predicted to be either non-targeting in the human genome, or (ii) to target another gene or genomic sequence, or (iii) invalid non-targeting control reagents that were predicted to target a human gene (Figure 1.8) (Byrne et al., 2019). The use of such wrongly identified reagents does not align with published results (Figure 1.8) (Byrne et al., 2019; Byrne et al., 2022). These errors could reflect genuine human errors, or they could reflect misconduct and research paper mill activity, as some of these errors seem unlikely to be made by experts (Park et al., 2022).

	Claimed status	Verified status	Consequences
Wrongly identified reagents			
Claimed targeting yet wrong target	5'- gene X -3'	5'- gene Y -3'	Irrelevant and/or impossible data
Claimed non-targeting yet targeting	5'- no target -3'	5'- gene X -3'	Use of invalid negative control
Claimed targeting yet non-targeting	5'- gene Y -3'	5'- no target -3'	Impossible data
Non-verifiable reagents			
Reagent with unclear claimed identifier	5'- ? -3'	5'-?-3'	Data cannot be reproduced with described methods

Figure 1.8. Wrongly identified nucleotide sequence identity error types (red box) and non-verifiable reagents (blue box). Error types are at the left, claimed versus verified status is shown in the centre panel and the experimental consequences are shown at the right. Upper panel adapted from Byrne et al. (2021).

A semi-automated fact-checking tool, Seek and Blastn, was developed to fact-check the identities of nucleotide sequence reagents at scale (Labbé et al., 2019). Subsequent analyses revealed problematic papers that incorrectly identified nucleotide sequence reagents, covering a broad range of topics, including the examination of gene functions in the context of chemotherapeutic resistance and the function of ncRNA genes such as *miR-125* (Park et al., 2022). Problematic papers were mostly published in low to moderate IF journals, with a few examples in higher IF journals (Byrne & Labbé, 2017; Labbé et al., 2019; Park et al., 2022). This result partly reflects the skewed distribution of journal IFs (Romanovsky, 2019; Siler & Larivière, 2022), where high IF cancer research journals, defined as an IF greater than

7.0, correspond to approximately 20% of cancer research journals (Kempf et al., 2018).

Despite the limitations of interpreting IF as a measure of quality (Siler & Larivière, 2022), high IF journals are prestigious and influential within their respective fields (Al-Awqati, 2007; Callaham et al., 2002), and thus their papers are expected to be of high quality. However, in our recent study (Pathmendra et al. 2024), we found 38% of all original 2020 papers in *Molecular Cancer* (2020 IF = 27.4) contained wrongly identified nucleotide sequence reagents. This suggests that, irrespective of journal prestige and IF, wrongly identified nucleotide sequence reagents may represent an unrecognised problem in human gene research.

1.2.8 Plagiarism and image manipulation in gene research

Queries about gene research integrity are not limited to materials and methodology, but also pertain to the results themselves, where one such concern is plagiarism. Generally, plagiarism can be defined as “theft, taking material authored by others and presenting as someone else” (Masic, 2012). In scientific publications, plagiarism can be categorised as the reuse of complete or partial elements of previous publications without citation or the borrowing of ideas, opinions and content without citation (Masic, 2012; Roig, 2012). Plagiarism can occur through human error, as well as intellectual dishonesty and/or misconduct (Mohammed et al., 2015). Biomedical researchers have described encountering complete plagiarism of existing papers, where one publication is directly duplicated with minor changes, without any discussion of the more recent

paper representing a reproduction or replication (North, 2023). However, a more common manifestation of plagiarism in gene research occurs where images of experimental data, such as Western blots or cellular assays, are plagiarised and/or manipulated (Figure 1.9) (Bik et al., 2016; Bik et al., 2018; Christopher, 2018; Christopher, 2021; Rossner & Yamada, 2004).

Prominent examples of image integrity analyses have been published by Elisabeth Bik and colleagues (Bik et al., 2016; Bik et al., 2018), who discovered image integrity concerns associated with plagiarism (within and between papers) and what appears to be deliberate image manipulation in a range of research papers. In Bik et al. (2016), the researchers screened 20,621 papers published across 40 biomedical journals, where 3.8% papers contained problematic figures, generally of Western blots or microscopic images. The authors categorised the problematic image duplications into three categories: i) simple duplications across multi-panel images, ii) duplication with repositioning, where one image was shifted, rotated and reversed and plagiarised as another figure, and iii) duplication with alteration, where image elements were deliberately adjusted and manipulated to create supposedly different images (Figure 1.9) (Bik et al., 2016).

The authors speculated that simple duplications were likely associated with honest error, while the latter two categories were potentially associated with research misconduct (Figure 1.9) (Bik et al., 2016). Since then, publishers such as FEBS Press have included image integrity screening in their editorial workflows (Christopher, 2018). Problematic images have also been proposed as a sign of fake scientific

manuscripts, where experts have recalled seeing recurring duplications of images from Western blot experiments, suggesting that such image plagiarism and manipulation could be a sign of manuscripts from research paper mills (Christopher, 2021).

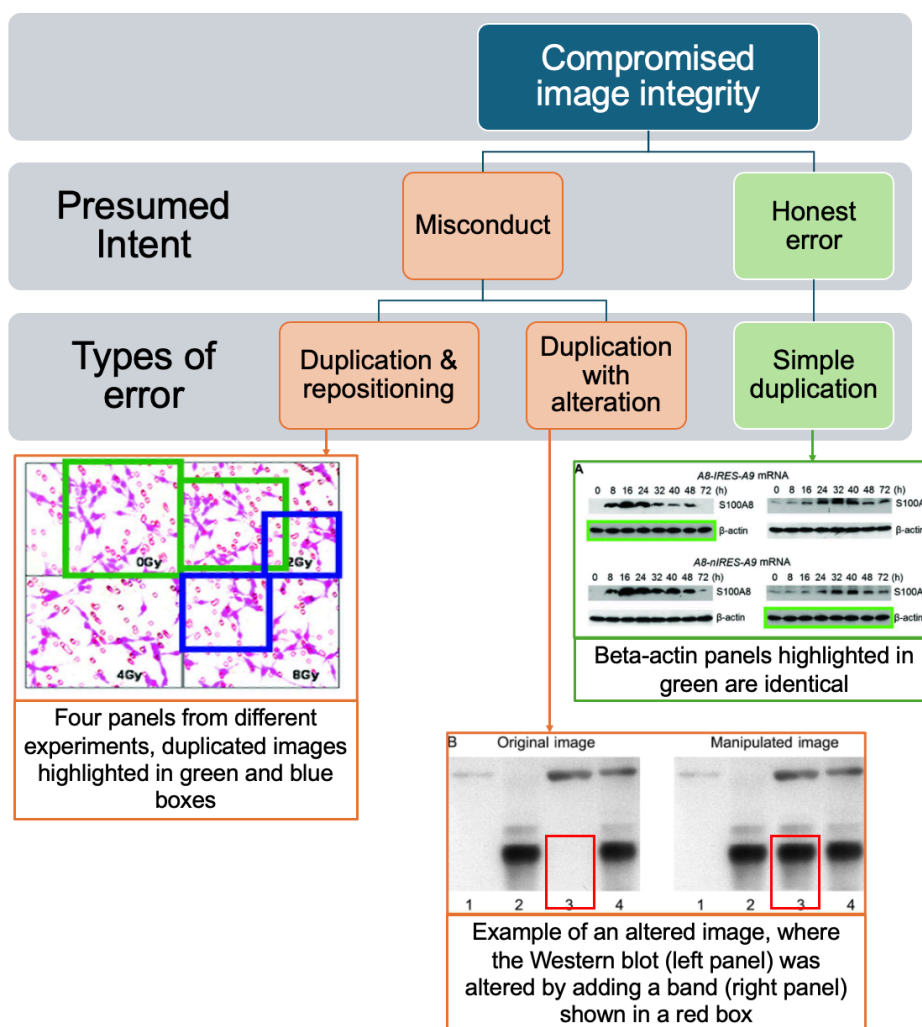


Figure 1.9. Explanation of the three image integrity error types identified by Bik et al. (2016). Green boxes represent simple duplications potentially associated with honest error, whilst orange boxes represent errors potentially associated with misconduct. Examples shown in the right and left panels are from Bik et al. (2016), whereas the example shown in the middle panel is from Rossner & Yamada (2004). Explanations of the image errors are shown below each image.

1.3 Safeguarding publication integrity

Safeguarding publication integrity relies on the self-corrective capacity of science, where researchers are expected to be stewards of the scientific record, ensuring its integrity (Merton, 1942). Integrity can be safeguarded via actions pre- and post-publication (Figure 1.10)

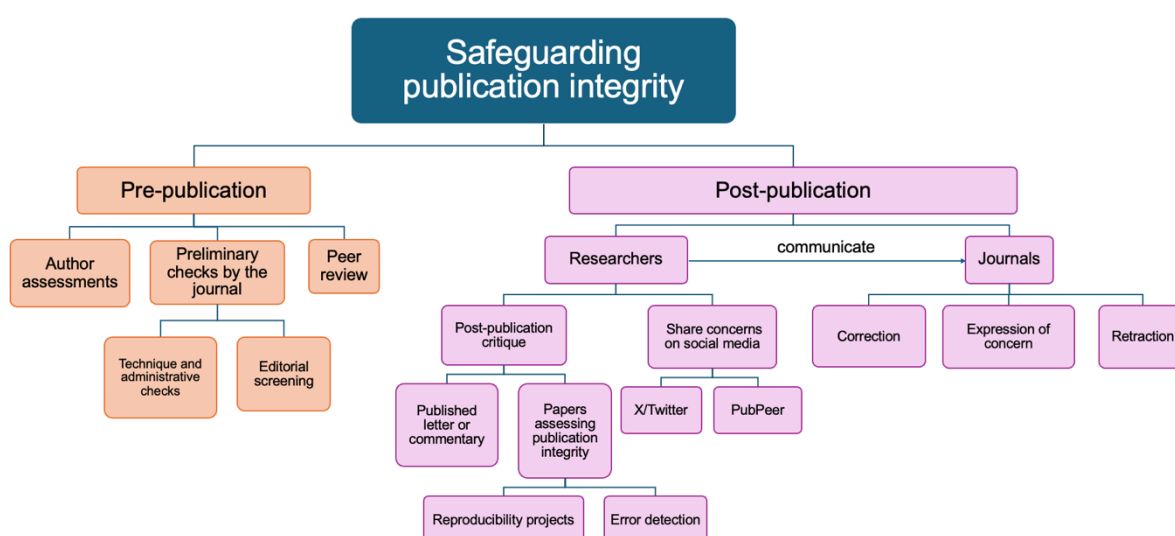


Figure 1.10. Diagram summarising methods to safeguard publication integrity, categorised as measures adopted pre-publication (orange) or post-publication (purple).

1.3.1 Pre-publication actions to safeguard publication integrity

Once a manuscript has been finalised, authors will submit it to a specific journal that will then conduct preliminary quality assessments, potentially followed by peer review

(Bolland et al. 2025). It is expected that concerns about manuscript integrity will be identified and addressed during the review process. However, peer review is conducted on a voluntary basis, with limited or no guidance or standards (Lipworth et al., 2011), and as discussed earlier, can be compromised by bad actors (Matusz et al., 2025; Van Noorden, 2023).

There have been some recent developments in peer review, including an emphasis on 'open peer review' or transparency of the peer review process, so that readers can evaluate how the manuscript was assessed prior to publication (Tennant, 2018). Another approach is the 'publish, review, curate' model (Hyde et al., 2022). This model involves publishing first, as a dataset or preprint that is then reviewed. The journal curates all preprints, reviews, and reports that will be attached to the final publication (Eisen et al., 2020). This process is designed with the aim of complete transparency, to counteract the exploitation of peer review by bad actors and provide researchers with more information about how publications were assessed (Hyde et al., 2022). Preprint servers such as bioRxiv (Sever et al., 2019) allow authors to share non-reviewed manuscripts. However, research indicates that authors post preprints close to publication or after submission to a journal, thereby limiting prepublication exposure (Anderson, 2020).

In tandem with innovations in peer review and a greater emphasis on transparency, publishers have also increased their efforts to critically assess manuscripts (Byrne et al., 2022). One example is the cross-publisher STM Integrity Hub that provides education, shared tools and workflows leveraging known paper mill features to detect

problematic submissions (COPE & STM, 2024; Else, 2022; Parker et al., 2024). However, as Richardson et al. (2025) estimated, the number of suspected paper mill-authored publications continues to grow, suggesting that current prepublication efforts are insufficient to prevent unreliable manuscripts from being published.

1.3.2 Post-publication actions to safeguard publication integrity

Crucial to ensuring publication integrity is the correction of the scientific record, while some errors can be resolved through corrections (Pierson, 2020), papers should be retracted when they are found to be fundamentally inaccurate or unreliable (Wager et al., 2009) (Figure 1.10). If there are insufficient reasons to retract, but nonetheless serious doubts pertaining to the paper's validity or reliability, then an expression of concern can be published as a warning (Noonan & Parrish, 2008).

The process of seeking post-publication corrections is inefficient and slow, as demonstrated by Byrne et al (2021), where retractions of gene research publications required 2-30 months, corrections required 19-28 months and expressions of concerns required 17-21 months to be published. Other researchers who have attempted to correct the published record have shared similar experiences, where publisher responses to queries about publication integrity are often vague and slow (Parker et al., 2022). As such, the existing post-publication correction system, which publishers primarily administer, is not addressing the increasing problem of unreliable research publications.

Alternatives to post-publication corrections include replicability and reproducibility projects (Errington et al., 2021a; Errington et al., 2021b), and studies of error detection (Bik et al., 2016; Labbé et al., 2019; Park et al., 2022). However, these studies are time-consuming and resource-intensive (Byrne et al., 2022; National Academies of Sciences, Engineering, and Medicine, 2019), making them a non-viable method for combating the rise of papers with poor publication integrity.

Researchers can also leverage social media platforms such as Twitter/X and PubPeer to seek post-publication corrections (Brookes, 2025; Ortega, 2022). PubPeer was designed as an online platform for post-publication commentary (Townsend, 2013); however, a significant portion of posts represent queries about potential misconduct (Ortega, 2022). It is hoped that PubPeer posts could raise awareness of publications with integrity concerns, leading authors and/or publishers to take appropriate action (Townsend, 2013). However, retrospective analysis of PubPeer comments and associated journal actions suggests that PubPeer posts may have limited impact on post-publication corrections (Ortega & Delgado-Quiros, 2023). In saying this, the STM Integrity Hub has recently included PubPeer comments in its shared screening tool, indicating the potential for more action by journals and publishers towards concerns raised on PubPeer.

1.4 Rationale for thesis and knowledge gaps

While integrity and trust remain core principles of research, increasing numbers of unreliable publications (Park et al., 2022; Pathmendra et al., 2024; Lou et al., 2024) and the growth of entities like research paper mills that enable systematic research fraud (Byrne et al., 2022; Richardson et al., 2025) demand further investigations. This thesis will address these issues by studying publication integrity from multiple perspectives.

1.4.1 Publication integrity of the human circRNA literature

Our previous work by Park et al. (2022) identified 40 problematic papers in *Gene* and *Oncology Reports* describing wrongly identified nucleotide sequences that also referred to ncRNAs in their titles. Targeted screening of 163 *miR-145* papers published from 2014 to 2019 found that 19% described wrongly identified nucleotide sequences, including papers published in journals with an IF above 7. Given that some problematic ncRNA papers were highly cited, we speculated that ncRNAs might broaden the possibilities for fabricating gene research papers. The inclusion of ncRNAs as research topics could offer a sense of novelty and complexity that makes ncRNAs attractive to paper mills that may be targeting high IF journals.

To verify whether nucleotide sequence reagent errors are common in papers in high IF journals, we screened all original papers published in *Molecular Cancer* during 2014, 2016, 2018, and 2020 (Pathmendra et al., 2024). We found that 18% (91/500) of the original papers described wrongly identified nucleotide sequence reagents,

where half of these papers referred to ncRNA gene(s) (particularly miRNAs and circRNAs) in the title. We then conducted a keyword search to identify 2020 papers that studied miRs and/or circRNAs in another high-IF journal, *Oncogene*. Corroborating the results for *Molecular Cancer*, we found approximately half of the screened papers to be problematic (Pathmendra et al. 2024).

In this thesis, we first developed novel fact-checking methodologies to verify the identities of circRNA reagents in papers published in *Molecular Cancer* and *Oncogene*. Chapter 2 further extends these previous results by verifying reagent identities in the original 2022 circRNA papers in high-IF journals. In doing so, we aimed to build consensus on appropriate standards for circRNA targeting reagents for different molecular techniques used in circRNA research and to identify problematic 2022 circRNA papers published in high IF journals.

1.4.2 Do PubPeer posts influence post-publication corrections?

Byrne et al. (2021) found that describing a particular type of wrongly identified nucleotide sequence reagent to journals via email yielded inefficient post-publication corrections. Although researchers have leveraged PubPeer to flag integrity concerns (Ortega, 2022), to our knowledge, no study has examined whether PubPeer posts influence post-publication corrections. Similarly, no previous study has examined how authors and journals respond to descriptions of nucleotide sequence reagent errors on PubPeer. Chapter 3 aims to address these gaps in the literature.

1.4.3 Publication Integrity: A Qualitative Perspective

Despite ECRs and postgraduate students often being targeted with interventions to improve the culture around research integrity (Abdi et al., 2021a), to our knowledge, no previous study has examined postgraduate student and/or ECR awareness, experiences, or education in publication integrity. The existing research in this area either lacked a primary focus on ECR and student perspectives (Schmidt, 2021), assessed experiences around reproducibility as opposed to publication integrity (Lubega et al., 2023), or focused on ECRs and students as contributors and hence perpetrators of poor publication integrity (Hofmann et al., 2020). As such, there is a need to qualitatively examine the contexts in which postgraduate research students and ECRs operate when considering the integrity of the literature. Chapter 4 addresses this gap through a qualitative online survey of ECRs and postgraduate research students, examining their awareness, understanding, experiences, and education in relation to publication integrity.

1.5 Thesis aims

To address the gaps in knowledge described (Section 1.4), this thesis has three aims:

1. To assess the publication integrity of human circRNA research publications published in high-IF journals.
2. To identify whether posting queries of wrongly identified nucleotide sequence reagents on PubPeer promotes post-publication correction.
3. To determine and understand ECRs' and postgraduate research student awareness, and experiences of publication integrity and their perceived impacts of unreliable research publications.

Chapter 2: The publication integrity of circRNA papers in high IF journals

2.1 Introduction

The study of genes and their dysregulation in disease has been central to understanding key biological mechanisms and the development of novel treatments (Byrne et al., 2022; Loganathan & Doss, 2023). We can broadly divide genes into protein-coding and non-coding genes (Amaral et al., 2023). Protein-coding genes are transcribed into mRNA, which is then translated into proteins, whereas non-coding genes are transcribed into RNA but not translated. In the past decade, much attention has been focused on non-coding genes due to their regulatory roles and potential as therapeutic targets or biomarkers for various diseases, including cancer (Byrne et al., 2022; Loganathan & Doss, 2023; Mattick et al., 2023; Poller et al., 2023).

One type of ncRNA that has gained attention in human gene research are circRNAs (Yehui et al., 2024). As shown in Panda et al. (2017) and Nielsen et al. (2022), circRNAs are formed by alternative splicing of RNA transcripts where the 5' and 3' ends are covalently joined to form a closed circular construct (as opposed to the usual linear RNA). The term 'circular RNA' was first introduced in the context of viroids, a type of plant pathogen (Sänger et al., 1976). The earliest identification of human circRNAs was reported by Nigro et al. (1991), who identified four circRNAs from the *DCC* gene and postulated that circRNAs are implicated in creating transcriptomic diversity. Following this, Cocquerelle et al. (1993) identified circRNA from *ETS-1* as

specific RNA transcripts, denoting them as ‘mis-spliced’ molecules with potential functionality in human cells (Cocquerelle et al., 1993).

Subsequent early molecular studies in yeast (Schindewolf et al., 1996), mice/rats (Capel et al., 1993; Zaphiropoulos, 1996) and human (Surono et al., 1999) cells identified and characterised endogenous circRNAs as products from scrambling exons, exon-shuffling or as “non-linear mRNAs” (Dixon et al., 2005). Developments in high-throughput sequencing methods and computational pipelines (Gondane & Itkonen, 2023; Jeck & Sharpless, 2014) led to key studies that identified several thousands of circRNAs expressed in metazoans, including human, rat and nematodes (Jeck et al., 2013; Memczak et al., 2013; Salzman et al., 2012). In tandem, studies also discovered the biological capacity of circRNAs, for example, where CDR1As/ciRS-7 was described to bind and regulate miRNA (Hansen et al., 2013), or where circRNAs were described to be upregulated in neuronal differentiation (Rybak-Wolf et al., 2015).

The establishment of novel methods, such as the use of RNase R to digest linear RNA and enrich circRNA (Jeck et al., 2013; Memczak et al., 2013), bioinformatic pipelines to identify unique characteristics, such as the back splice junction (BSJ) (Zeng et al., 2017), and reference databases (Xu, 2017) have made circRNA research more accessible. Since then, there has been an explosion of research on circRNAs (Yehui et al., 2024), and their capacity to function as protein templates, decoys, scaffolds and/or recruiters, and regulators of transcripts including miRNAs (Panda et al., 2017; Zhou et al., 2020). Consequently, there has been much discussion of circRNA being

implicated in regulating cellular homeostasis (Fischer & Leung, 2017), cancers such as head and neck, prostate, breast or lung cancers (Kristensen et al., 2022; Vo et al., 2019), and diabetes, cardiovascular and neurodegenerative diseases (Aufiero et al., 2019; D'Anca et al., 2022; Verduci et al., 2021).

However, in the context of the rising reproducibility crisis (Section 1.1) and other broader issues of publication integrity across disciplines, including biomedicine (Chapter 1.2) (Byrne et al. 2022), a meteoric rise in circRNA publications from 35 papers in 2015 to 2025 papers in 2021 (Yehui et al., 2024) potentially warrants concern. As discussed (Sections 1.2.3-1.2.5), gene research is susceptible to imitation and targeting by paper mills or other non-genuine actors (Byrne et al., 2022). CircRNA research is an evolving field with decentralised and non-standardised reference databases (Vromman et al., 2021), a lack of consensus on naming nomenclature (Seal et al., 2020), and debated analytic methodologies (Digby et al., 2024; Drula et al., 2024; Pandey et al., 2020; Robic & Kühn, 2025; Singh et al., 2024). Furthermore, as proposed (Section 1.2.5, Figure 1.6), studies of circRNA provide an additional layer of complexity to gene research, with experiments and results that could be attractive to high-impact journals. Hence, we suspect that paper mills might find circRNA research an attractive target.

A recent analysis of original papers published in *Molecular Cancer* in 2014, 2016, 2018, and 2020, as well as *Oncogene* in 2020, revealed papers describing circRNAs that also disclosed wrongly identified nucleotide sequence reagents, potentially resulting in unreliable results (Pathmendra et al., 2024). We also encountered a subset

of circRNA targeting reagents that were difficult to verify due to a lack of specific targeting information, because the claimed circRNA could not be independently identified in publicly available reference databases (Pathmendra et al., 2024). In this chapter, we therefore aim to assess the integrity of circRNA research published in high IF journals. Firstly, we will examine the subset of papers with nucleotide sequence reagents claimed to target circRNAs in articles in *Molecular Cancer* and *Oncogene* and describe the consequent fact-checking methodology we developed. Following on, we will fact-check reagent identities in i) papers that mentioned circRNAs in their title retracted before September 2023 and ii) all original papers mentioning circRNA in their titles that were published in 2022 in journals with an IF above 7. Given that cell lines and nucleotide sequence reagents are widely used in molecular research and form a cornerstone of fundamental biological techniques, publications should accurately report these reagents. The use of genome/transcriptome alignment algorithms, such as BLAST, is a widely taught skill in undergraduate biology (Niepielko & Shumskaya, 2021; Unger & Rollins, 2022) and is known to most molecular researchers. As such, we aimed to use widely applied techniques that any molecular researcher could apply to assess the claimed identities of key reagents in circRNA publications in high IF journals, to identify possible issues of integrity and quality facing this field.

2.2 Methods

2.2.1 Identification of Papers

2.2.1.1 *Molecular Cancer* and *Oncogene* corpora

Papers published in *Molecular Cancer* were retrieved via the Web of Science using the search criteria: PY = “2014, 2016, 2018, 2020”, PT = “MOLECULAR CANCER”, AND DT = “Article”. Paper titles were used as search queries on the *Molecular Cancer* website to obtain PDFs and supplementary files. Based on features of some *Molecular Cancer* papers with wrongly identified nucleotide sequence(s), selected *Oncogene* papers were retrieved via the Web of Science using the search criteria: PY = “2020”, PT = “ONCOGENE”, DT = “Article”, and keywords = [(“Circular RNA*.mp.” OR “circRNA*.mp.”) OR (“microRNA*.mp. OR “miR*.mp.”)]. *Oncogene* paper titles were used as search queries to obtain PDFs and supplementary files through the University of Sydney library.

2.2.1.2 Retracted circRNA papers in high impact factor journals corpus

A corpus of retraction notices of papers with mentions to circRNA in their title and/or abstract were retrieved via Web of Science using the search criteria: Keywords = "circular RNA*" (Title) or circRNA* (Title) or "hsa_circ*" (Title) or "hsa-circ*" (Title) or "hsacirc*" (Title) or "circ* RNA*" (Title), DT = “Retracted Publication”. This search was conducted on the 27th September 2023. The results were exported to InCites (Clarivate), and a dataset of journals that published these retractions, along with their journal IF, was downloaded into Microsoft Excel. The journals with a 2022 IF \geq 7 were

used as an additional filter on the initial Web of Science search. The titles of retracted circRNA papers in high-impact journals (2022 IF \geq 7) were used as search queries on PubMed or the University of Sydney library to obtain publication PDFs and supplementary files.

2.2.1.3 CircRNA papers published in 2022 in high impact factor journals corpus.

A corpus of papers with mentions to circRNA in their title and/or abstract were retrieved via Web of Science using the search criteria: Keywords = "circular RNA*" (Title) or circRNA* (Title) or "hsa_circ*" (Title) or "hsa-circ*" (Title) or "hsacirc*" (Title) or "circ* RNA*" (Title), DT = "Article". This search was conducted on the 19th of September 2023. The number of original circRNA papers published per year from 1976 to 2022 and the number of circRNA papers according to Web of Science's "Countries/Regions" category per year were recorded in MS Excel. We then selected papers published in 2022 by adding the following filter to the Web of Science search: PY = "2022". The results were exported to InCites (Clarivate), and a dataset of journals with a 2022 IF was downloaded into Microsoft Excel. We identified journals with a 2022 IF \geq 7 and used these journal names as an additional filter in the initial Web of Science search to collate original circRNA papers published in high IF journals. The titles of these papers were used as search queries on PubMed or the University of Sydney library to obtain publication PDFs and supplementary files.

2.2.2 Visual Inspection

2.2.2.1 *Molecular Cancer and Oncogene corpora*

Each paper was visually screened and included for manual analysis if the study described the sequence of at least one nucleotide sequence reagent that was claimed to target a human circRNA or associated elements, such as promoters. Both the text and supplementary files were visually inspected to determine the claimed genetic and/or experimental identity of nucleotide sequence reagents. If the claimed identity was not evident or if nucleotide sequence reagents were claimed to target genes in species other than humans, the reagent was excluded from analysis. We included papers with post-publication corrections and retractions and verified reagents available in both the original and corrected reagent lists. The nucleotide sequences and claimed identities were extracted using copy-paste functions or manually transcribed from flat image files by eye into MS Excel.

2.2.2.2 Retracted circRNA paper in high IF journal corpus

Each retraction notice was visually screened, and the content of the notice was summarised in MS Excel. Each retracted paper and any supplementary files were visually screened as described in Section 2.2.2.1, with the additional step of also extracting details of cell lines. Cell lines that were claimed to be models of organisms other than humans were excluded. We verified the nucleotide sequence reagents available in the most updated, corrected form of the publication as of 27th September 2023.

2.2.2.3 CircRNA papers published in 2022 in high impact factor journals corpus

We visually screened all collated papers' titles and abstracts to identify original circRNA research papers that investigated circRNAs in humans. Each circRNA paper was visually screened and included for analysis if the study described the sequence of at least one nucleotide sequence reagent that was claimed to target a wild-type human transcript or genomic region, or the use of human cell lines. Both the main text and supplementary files were visually inspected to determine the claimed genetic and/or experimental identity of nucleotide sequence and cell line reagents. If the claimed identity of nucleotide sequence reagents was not evident, the reagent was excluded from analysis. We also inspected the publication and supplementary files to determine the claimed identities of human cell lines. In the absence of clearly linked identifiers, the claimed identity was determined by analysing the context in which the cell lines were used across the paper.

2.2.3 Manual Verification of nucleotide sequence reagents claimed to target circRNAs.

All identities of non-modified nucleotide sequence reagents claimed to target a human gene, transcript or genomic region were confirmed as described in Park et al. (2022). Briefly, nucleotide sequence reagents were queried using Blastn (Altschul et al., 1990), BLAT (Kent, 2002), or the alignment tool available on miRBase (Griffiths-Jones et al., 2006). For reagents claimed to target miRNA, we manually aligned the nucleotide sequences with the claimed miRNA transcript available on miRBase, as described by

Park et al. (2022). Where necessary, sequence orientations were reversed or reverse-complemented using The Sequence Manipulation Suite¹. If the predicted identity did not match the claimed identifier, we examined synonymous identifiers or the corresponding chromosomal position of the claimed target disclosed by the study authors or identified via GeneCards (Stelzer et al., 2016), miRbase (Griffiths-Jones et al., 2006), and Ensembl (Harrison et al., 2024). If there was a mismatch between the claimed and predicted reagent identities, reagents were classified as wrongly identified, as described in Section 2.2.4. For circRNA reagents, since no existing guidelines were available, we developed new methods, as described in Sections 2.2.3.1-2.2.3.3.

2.2.3.1 Verification of RT-PCR primers claimed to target circRNAs

RT-PCR of circRNAs requires two sets of RT-PCR primers: convergent and divergent primers (Dudekula et al., 2016; Nielsen et al., 2022; Zhong et al., 2018). Convergent primers function similarly to conventional RT-PCR primers, amplifying linear transcripts from the host gene (Dudekula et al., 2016; Nielsen et al., 2022; Zhong et al., 2018). Convergent primers were verified as conventional RT-PCR primers claimed to target protein-coding genes and/or lncRNA, depending on the gene from which the circRNA originated (Dudekula et al., 2016; Nielsen et al., 2022; Pathmendra et al., 2024; Zhong et al., 2018).

¹ https://www.bioinformatics.org/sms/rev_comp.html

For divergent RT-PCR primers claimed to target circRNAs, forward and reverse primers were queried on CircPRIMER (Zhong et al., 2018) using standard settings (Figure 2.1). RT-PCR primers were noted as correctly targeting if CircPRIMER aligned both forward and reverse primers to the claimed circRNA(s) such that they faced towards and were predicted to amplify the BSJ (Figure 2.1). If CircPRIMER produced no output, we then checked whether the specific transcript of the claimed circRNA could be identified through the disclosure of a specific circRNA identifier or information on the circRNA, such as length, BSJ sequence and/or chromosomal location that could be queried on circBASE (Glažar et al., 2014) or circATLAS (Wu et al., 2020). If the claimed circRNA transcript could not be identified, and thus we could not predict the BSJ, the divergent RT-PCR primers were classified as NV (Pathmendra et al., 2024; Patop & Kadener, 2018). If the specific circRNA transcript was identified, we either manually aligned the primer to the transcript sequence and its reverse complement using MS Word and/or queried primers using the BLAT function of circBASE (Glažar et al., 2014). We uploaded sequences to an online tool, 'The Sequence Manipulation Suite' that provided the sequence in reverse complement orientation. Claimed divergent primer sequences were classified as wrongly identified if they did not amplify the BSJ as predicted (Figure 2.1). These primers were subjected to further analysis as described in Park et al. (2022) to classify these reagents according to the error categories to be explained in Section 2.2.4.

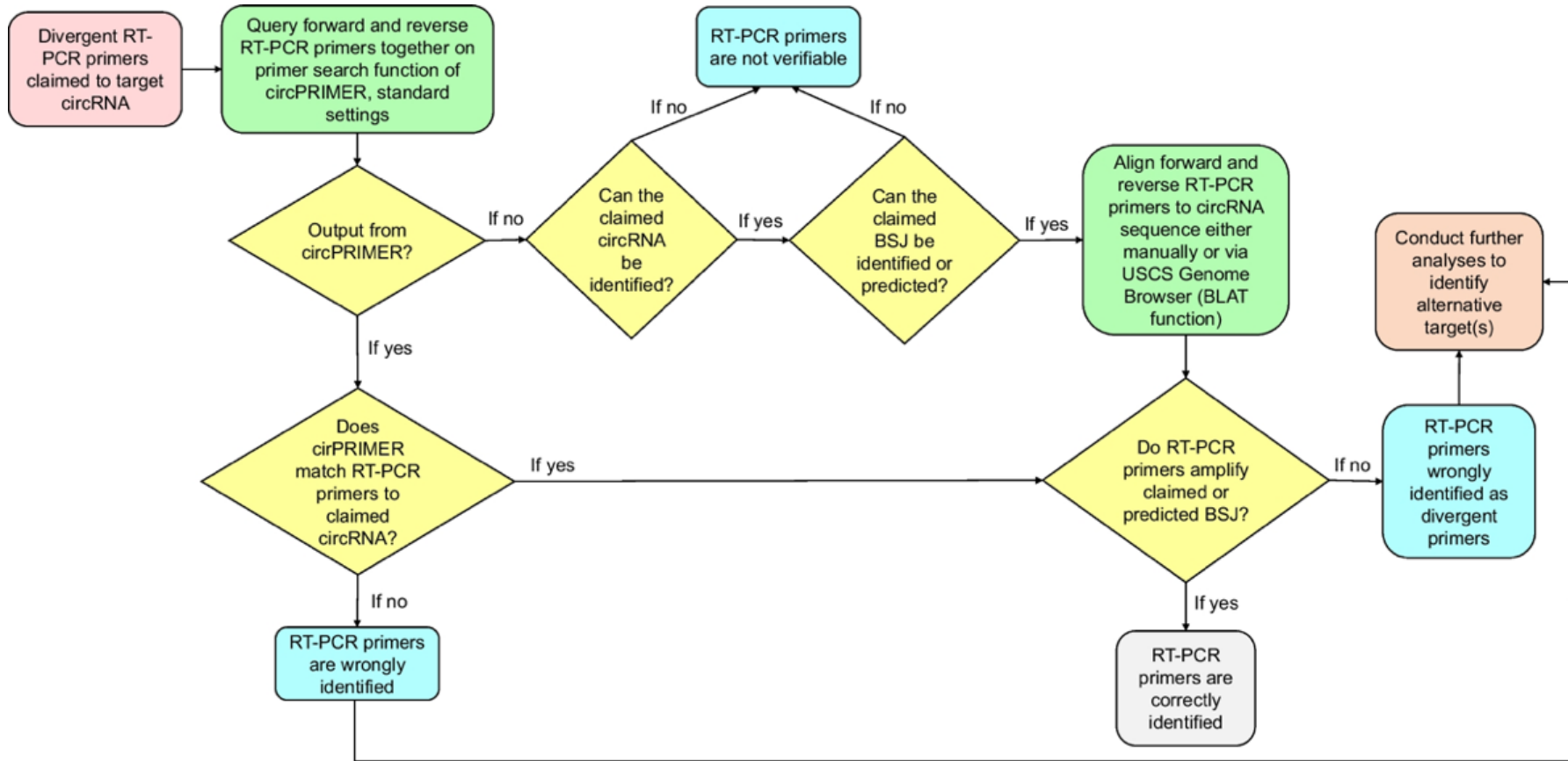


Figure 2.1. A flow chart summarising the manual verification of divergent RT-PCR primers claimed to target human circRNAs (Pathmendra et al., 2024).

2.2.3.2 Verification of other circRNA targeting reagents

Single sequence reagents such as si/shRNAs function by targeting the BSJ of the claimed circRNA target (Dudekula et al., 2016; Nielsen et al., 2022). We first checked whether the claimed circRNA could be identified as described above (Section 2.2.3.1-2). If the claimed circRNA transcript could not be identified, meaning that we could not reconstruct the BSJ, or if the annotation of the claimed circRNA was unclear, the reagents were classified as NV. Upon identifying the claimed circRNA transcript, the sequences were manually aligned against the BSJ sequence (Figure 2.2). Single reagents, including shRNAs/siRNAs, were classified as correctly targeting if they showed between 5-16-nucleotide matches to both sides of the BSJ (Dudekula et al., 2016). If a claimed circRNA reagent showed 100% identity over 17 consecutive nucleotides with linear transcripts from the host gene, the reagent was classified as wrongly identified, as such reagents were predicted to not discriminate between circular and linear isoforms. If a reagent showed identity to the claimed BSJ with < 5nt identity on at least one side of the BSJ or showed no identity to the claimed BSJ, the reagent was also noted as being incorrectly identified. Wrongly identified reagents were subjected to further analysis as described (Park et al., 2022) to classify them according to the error categories explained in Section 2.2.4.

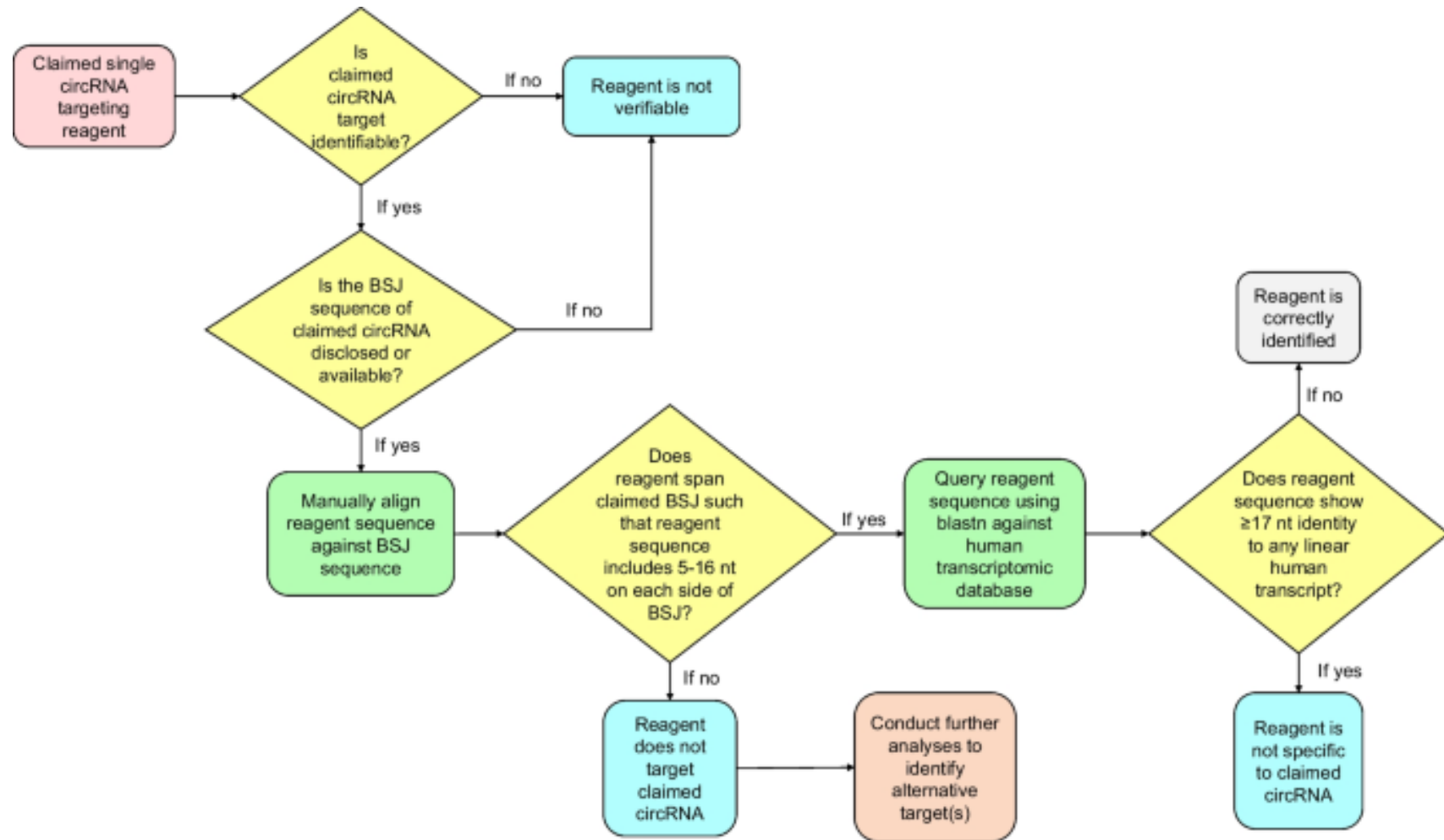


Figure 2.2. Flowchart summarising the manual verification of siRNAs, shRNAs, and other oligonucleotide probes claimed to target human circRNA (Pathmendra et al., 2024).

2.2.3.3 Verification of circRNA probes used in FISH, RNA-pull down and Northern blot

Single probes claimed to target circRNAs used in FISH (Fluorescence In-Situ Hybridisation) or ISH (In-Situ Hybridisation), and in RNA-pulldown or Northern blot experiments require longer consecutive sequence matches to the claimed target circRNA on either side of the BSJ (Das et al., 2021; Zirkel & Papantonis, 2018) compared with targeting requirements for siRNAs (Section 2.2.3.2, Figure 2.3). We first checked whether the claimed circRNA could be identified (Section 2.2.3.1). All probes were assumed to target the BSJ of the claimed circRNA, unless stated otherwise by the study. We then verified whether the oligonucleotide probes used in FISH, RNA-Pulldown, or Northern Blot satisfied the criteria outlined in Table 2.1 and recorded the number of nucleotides that showed identity to each side of the claimed BSJ in MS Excel. However, methods did not offer clear guidance on the sequence matches required to ensure that reagents can discriminate between linear and circular RNA isoforms (Das et al., 2021; Zirkel & Papantonis, 2018). As such, any probes that showed matches to either side of the claimed BSJ but did not meet the ideal probe requirements outlined in Table 2.1 were not reported as wrongly identified. Any FISH/ISH or RNA-pulldown probes that were claimed to target the BSJ but were predicted to match sequences on only one side of the BSJ were noted as wrongly identified.

Table 2.1. Targeting criteria for circRNA targeting probes used in FISH/ISH, RNA-pull down, and Northern blot assays

Experiment	Targeting criteria	Reference
FISH	<i>BSJ Probe</i> : 55 nt length, 22-24nt match to both sides of BSJ <i>Intronic probes</i> : three or four individual probes mapping to circRNA intron(s) in cases where circRNA includes introns	Zirkel and Papantonis, (2018)
	Small FISH probes targeting linear genes are expected to show 18-22nt match to claimed target	Gaspar et al. (2017)
RNA-Pulldown	<i>BSJ Probe</i> : ≥ 30 nt, ≥ 15 nt match to both sides of BSJ	Das et al. 2021,
	Probe length can range from 20-40nt, equivalent complementarity to both sides of BSJ	Gabryelska et al. 2024
Northern Blot probes	Longer probes: 100-500nt, used in RNase H assays Smaller riboprobes: 30-100nt	Schneider et al. 2018
	<i>DIG-labelled riboprobes</i> : Attach T7 or SP6 sequence to 5' end of reverse primer (18-22nt match to circRNA antisense transcript) Probes can target BSJ (equivalent matches to both sides of BSJ) or be complementary to circRNA transcript	

2.2.4 Classification of wrongly identified reagents according to error categories

Wrongly identified nucleotide sequence reagents were classified according to previous error categories: i) claimed targeting reagents that were predicted to target another human gene or genomic sequence, ii) claimed targeting reagents that were predicted to be non-targeting in human, and iii) claimed non-targeting control reagents that were predicted to target a human gene or transcript (Labbé et al., 2019; Park et al., 2022). Wrongly identified circRNA targeting reagents were categorised according to these error types as summarised in Table 2.2.

Table 2.2. Summary of wrongly identified circRNA targeting reagents according to established nucleotide sequence reagent error types.

Error Type	Explanation
Claimed targeting reagents that were predicted to target another human gene or genomic sequence	Claimed divergent primer predicted to amplify linear RNA as convergent primers
	Claimed circRNA targeting siRNAs/shRNAs predicted to not discriminate between linear and circular isoforms.
	Claimed circRNA targeting reagents predicted to target a different gene/circRNA
Claimed targeting reagents that were predicted to be non-targeting in human	Claimed circRNA targeting reagent predicted to be non-targeting in humans (including reagents that show < 5nt of identity on either side of the BSJ)

2.2.5 Verification of cell lines

We verified the identities of human cell lines described in the retracted circRNA and 2022 circRNA corpora as described in Oste et al. (2024). Briefly, if the claimed cell line identity did not match the verified identity on Cellosaurus (Bairoch, 2018), we classified the cell line as wrongly identified. We flagged cell lines that were described as (potentially) contaminated by a different cell line or misclassified as problematic, if the original paper did not acknowledge i) the cell line's contaminated/misclassified status or ii) use of a contaminated/misclassified cell line as a study limitation (Oste et al., 2024). If the cell line was not indexed by Cellosaurus, the cell line identifier was queried on the ATCC catalogue² (American Type Culture Collection, n.d.) or the catalogue referred to by the original study. If the above approaches produced no results, the cell line identifier was queried on Google Scholar with terms such as “cells” or “cell line” to identify the earliest publication(s) describing the cell line. If no origin publication could be found for the cell line, further keyword searches were conducted on Cellosaurus and Google Scholar with variations in the spelling of the cell line identifier to identify the possible origin of the NV cell line, as described (Oste et al., 2024).

2.2.6 Additional publication analyses

For each eligible paper, we recorded the number and proportion of wrongly identified sequence reagents, and the numbers and identities of NV reagents. Publications that were not retracted were flagged as problematic if they included at least, one wrongly identified nucleotide sequence reagent. In addition to this, papers of the 2022-circRNA

² <https://www.atcc.org/>

corpus with at least one wrongly identified cell line were also deemed problematic. We reported papers with NV sequences and wrongly identified nucleotide sequence reagents separately. We categorised the claimed identities of analysed targeting nucleotide sequence reagents as targeting either protein-coding or ncRNAs or circRNAs or genomic, according to GeneCards (Stelzer et al., 2016), miRBASE (Griffiths-Jones et al., 2006), IncATLAS (Mas-Ponte et al., 2017), circBASE (Glažar et al., 2014), or circATLAS (Wu et al., 2020). We also calculated proportions of i) problematic papers (i.e. with wrongly identified nucleotide sequences reagents and/or cell lines), ii) verified sequences claimed to function in the context of circRNA, iii) wrongly identified sequences or cell lines, and iv) papers with NV reagents that also contained problematic features (i.e. wrongly identified nucleotide sequence reagents and/or cell lines).

We visually inspected publication titles to identify mentions of specific circRNAs, human cancer types, references to terms such as “sponging” and/or “axis”, and drug identifiers, which were confirmed through Google searches. The countries of origin and institutional affiliation were identified as described (Park et al., 2022). Where there was no numeric majority, the first author’s affiliation was used to decide the overall institutional affiliation and/or country of origin (Pathmendra et al., 2024). Citation numbers were collected according to Google Scholar on September 7, 2024 (for the *Molecular Cancer* and *Oncogene* corpora) and on September 25, 2024 (for the 2022-circRNA corpus). We also collected the 2022 journal IF for all papers analysed according to the journal metadata available on Clarivate InCites. Dates of submission and acceptance by the journal were also recorded as reported on the respective

journal webpage, for problematic papers across all corpora, and calculated the difference in time (in days) as a measure of time to acceptance.

We identified PubPeer comments (excluding all queries posted in relation to this thesis in chapter 3) for problematic papers using the publication title as queries on PubPeer³ (PubPeer Foundation, 2012). For the *Molecular Cancer* and *Oncogene* Corpora, we screened for PubPeer comments before April 2023 (to precede the start date of experiments in Chapter 3). For the retracted circRNA corpus, we examined PubPeer comments made before the retraction. For the 2022-circRNA corpus, we screened comments made before 23 September 2024. PubPeer comments were visually inspected to summarise the number and content of the PubPeer comments, the name of the poster if disclosed, whether publication authors had responded to the query, and the time of the first query posted on PubPeer (month and year). All calculations and data management were conducted on MS Excel.

2.2.6.1 Additional analyses of the retracted circRNA paper in the high impact factor journals corpus.

In addition to the publication analysis mentioned above, retraction notices were thematically coded based on the reason for the retraction and visually inspected for references to who initiated and/or authorised the retractions. We then recorded the proportions of retracted circRNA papers by reason for retraction, whether the reason for retraction was noted in any PubPeer comments made before the retraction date

³ <https://pubpeer.com/>

and who initiated the retraction. We also identified and calculated the proportion of retracted papers that described wrongly identified reagents (cell lines/sequences) from our analysis. Where circRNA papers were retracted for reasons cited in PubPeer comments, we calculated the time between the earliest PubPeer comment addressed in the notice and the publication date of the retraction notice as a measure of time to retraction from the first PubPeer query (in months) in MS Excel.

2.2.6.2 Additional analyses of circRNA papers published in 2022 in high impact factor journals corpus.

We calculated the total number of original circRNA papers published until 2022 according to publication year, as reported on Web of Science. For each year between 2012 to 2024, we calculated the proportion of original circRNA papers authored by teams where all authors were located in China, by selecting 'PEOPLES R CHINA' and excluding all other listed countries on the 'Countries/Region' filter on Web of Science. This search was conducted on 27 August 2025.

For each probe used for FISH, RNA-pull down, or Northern blot analyses that was verified to target the claimed circRNA, we recorded the length of identity flanking each side of the BSJ and compared it with published requirements (Table 2.1).

2.2.7 Statistical Analyses

We calculated a Spearman's rank correlation coefficient between the number of wrongly identified sequence reagents and the total number of verified nucleotide sequence reagents per paper. Fisher's Exact tests were used to compare proportions of papers with wrongly identified reagents (nucleotide sequences and/or cell lines) in the *Molecular Cancer* and 2022-circRNA corpora according to error status (presence of incorrect reagents), and country or institutions of origin. For the 2022-circRNA corpus, Mann-Whitney test was used to compare median journal IFs between papers included and excluded from the 2022-circRNA corpus (to assess selection bias in terms of IF by excluding documents) and median numbers of citations and times to acceptance between papers with incorrect reagents (problematic cell lines and/or wrongly identified nucleotide sequences) and papers with correctly identified reagents. All statistical analyses were performed on GraphPad Prism 10. All graphs were produced on MS Excel or GraphPad Prism 10. Reported p-values have not been corrected for multiple comparisons.

2.3 Results

2.3.1 *Molecular Cancer* and *Oncogene* Corpora

Overall, 192 original papers were published in *Molecular Cancer* in 2018 and 2020, of which 77% (148/192) described at least one nucleotide sequence reagent claimed to target a non-modified human gene (Pathmendra et al. 2024). In 2018 and 2020, 14% (10/74) and 41% (30/74) of papers, respectively, described at least one nucleotide sequence reagent that was claimed to target at least one human circRNA (Figure 2.3). In contrast, no *Molecular Cancer* papers in 2014 (0/157) and 2016 (0/29) that were screened described sequences claimed to target human circRNA (Pathmendra et al., 2024).

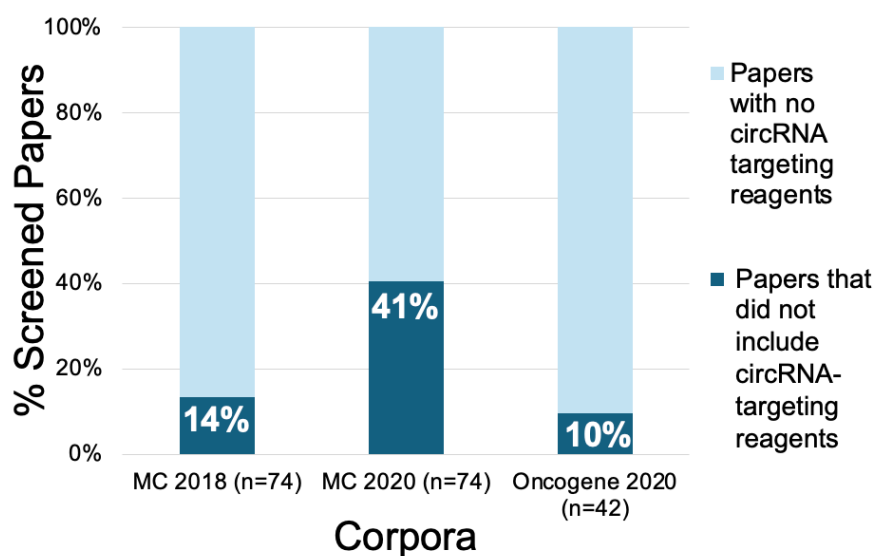


Figure 2.3. Percentages of screened papers (Y-axis) per corpora analysed (X-axis, corpora, n=number of papers screened per year). Papers were included for analysis as they described nucleotide sequence reagents claimed to target circRNA(s) (shown in dark blue, percentage values shown in white) or excluded from analysis (light blue).

MC = *Molecular Cancer*.

Collectively, the 2018 and 2020 papers with circRNA targeting reagents reported the use of 1,472 nucleotide sequence reagents whose identities were verified, with a median number of 21 nucleotide sequences per paper in 2018 (n=10, Range: 2-161) and 33 nucleotide sequences per paper in 2020 (n=30, Range: 2-103), respectively (Figure 2.4A). One third (484/1472, 33%) of these nucleotide sequence reagents were claimed to target human circRNAs (Figure 2.4B). The median number of circRNA reagents studied per 2018 *Molecular Cancer* paper that described circRNA targeting reagents was 8 circRNA reagents/paper (range: 2-50, n=10), and in 2020, 9 circRNA reagents/paper (Range: 1-48, n=30) (Figure 2.4C).

We identified 42 papers published in *Oncogene* in 2020 using a targeted keyword search with the terms “miR” and “circRNA”. Four papers (4/42, 10%) described the use of at least one nucleotide sequence reagent claimed to target at least one human circRNA (Figure 2.3). These four papers described 162 nucleotide sequence reagents, of which 58% (94/162) were claimed to target human circRNA(s) (Figure 2.4A, B). The median number of circRNA reagents/paper was 15 (range: 2-62, n=4) (Figure 2.4C). New protocols were developed to fact-check circRNA targeting reagents to recognise their specific targeting requirements (Figures 2.1, 2.2).

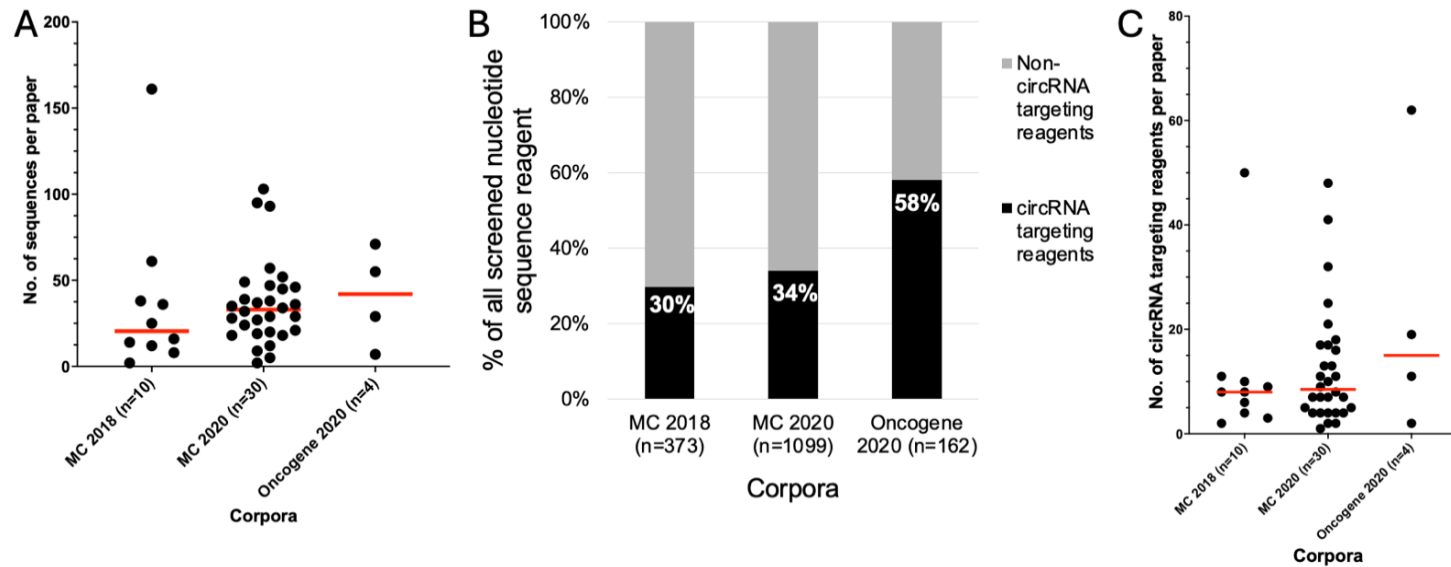


Figure 2.4. Summary of nucleotide sequences analysed in papers with circRNA targeting reagents in *Molecular Cancer* (MC) and *Oncogene*. A) Numbers of nucleotide sequences per paper included for analysis (Y-axis) according to the analysed corpus (X-axis, n=number of papers that described circRNA targeting reagents). B) Percentages of all nucleotide sequences analysed (Y-axis) according to analysed corpus (X-axis, n=number of sequences analysed per corpus) that were claimed target circRNAs (black, percentages shown in white) or claimed to target other genes or transcripts (grey). C) Numbers of nucleotide sequences per paper included for analysis (Y-axis) according to corpus (X-axis, n=number of papers that described circRNA targeting reagents). Included papers described at least one nucleotide sequence reagent that claimed to target at least one circRNA. Individual and median numbers of nucleotide sequences per paper are shown as black dots and red horizontal lines, respectively.

2.3.1.1 Wrongly identified nucleotide sequence reagents identified in *Molecular Cancer* papers with circRNA targeting reagents

Of the manually-verified 1,472 nucleotide sequences in papers with circRNA targeting reagents, 61 (61/1,472, 4.1%) nucleotide sequences were predicted to be wrongly identified (Table 2.3). This included claimed targeting reagents that were predicted to either target a different human gene or genomic sequence (35/61, 57%) or were predicted to be non-targeting in human (25/61, 41%). We identified one invalid negative control reagent that was predicted to target a human gene (Table 2.3). Most (48/61, 79%) incorrect sequences were PCR primers, of which 54% (26/48) were claimed to target protein-coding genes, including their promoters (Table 2.3, Supplementary Table 1.1).

Of the 484 nucleotide sequence reagents claimed to target human circRNAs, 3.5% (17/484) were wrongly identified (Table 2.4), with similar proportions of wrongly identified PCR primers (8/17, 47%) and single probe reagents (9/17, 53%) (Table 2.4). Almost all (16/17, 94%) wrongly identified circRNA reagents were predicted to target a different human gene; 7/16 (44%) of these were single-sequence reagents that were not predicted to discriminate between circular and linear transcripts. Most of the non-specific single sequence circRNA reagents (6/7, 86%, Table 2.4) did not show identity to either side of the BSJ and instead mapped to sequences shared by linear and circular isoforms of the claimed circRNA host gene. One incorrect single sequence circRNA reagent was predicted to be non-targeting in human (Table 2.4).

Table 2.3. Wrongly identified nucleotide sequence reagents in *Molecular Cancer* and *Oncogene* papers that described at least one circRNA targeting reagent

	<i>Molecular Cancer</i>	<i>Oncogene</i>
Corpus description	Original 2018 and 2020 papers with at least one nucleotide sequence reagent claimed to target a human circRNA	Selected 2020 papers with at least one nucleotide sequence reagent claimed to target a human circRNA
No. papers	40	4
No. nucleotide sequence reagents analysed	1,472	162
Nucleotide sequence reagents analysed per paper, median (range)	31 (2-161)	42 (7-71)
Proportion (percentage) of wrongly identified nucleotide sequence reagents.	61/1,472 (4.2%)	7/162 (4.3%)
Proportion (percentage) of problematic papers	16/40 (40%)	3/4 (75%)
No. of wrongly identified nucleotide sequences per paper, median (range)	3 (1-11)	2 (1-4)
Proportion (percentage) of wrongly identified nucleotide sequence reagents according to error type		
Claimed targeting reagents that were predicted to target a different human gene/genomic sequence	35/61 (57%)	3/7 (43%)
Claimed targeting reagents that were predicted to be non-targeting in human	25/61 (41%)	4/7 (57%)
Claimed non-targeting reagents that were predicted to target a human gene	1/61 (1.6%)	0/7 (0%)
Proportion (percentage) of wrongly identified nucleotide sequence reagents according to reagent type		
PCR primers	48/61 (79%)	1/7 (15%)
Single sequence probes	13/61 (20%)	6/7 (86%)
Proportion (percentage) of wrongly identified nucleotide sequence reagents according to claimed identity		
Protein-coding genes (including promoters)	26/61 (43%)	0/7 (0%)
Other genomic targets	3/61 (4.9%)	0/7 (0%)
miRNAs (including promoters)	13/61 (21%)	1/7 (14.3%)
CircRNAs	17/61 (28%)	6/7 (86%)
Other ncRNAs	1/61 (1.6%)	0/7 (0%)
Non-targeting	1/61 (1.6%)	0/7 (0%)

Table 2.4. Wrongly identified and non-verifiable (NV) circRNA targeting reagents identified in the *Molecular Cancer* and *Oncogene* corpora.

	<i>Molecular Cancer</i>	<i>Oncogene</i>
Total reagents analysed (n=)	1,472	162
Proportion (percentage) of nucleotide sequence reagents claimed to target circRNAs	484/1,472 (33%)	94/162 (58%)
circRNA targeting nucleotide sequence reagents analysed per paper, median (range)	8 (1-50)	15 (2-62)
Proportion (percentage) of claimed circRNA targeting reagents that were wrongly identified.	17/484 (3.5%)	6/94 (6%)
<i>Proportion (percentage) of wrongly identified circRNA reagents according to error types</i>		
Claimed circRNA targeting reagents predicted to target a different human gene or circRNA	16/17 (94%)	2/6 (33%)
Claimed to target circRNA but predicted to not discriminate between circular and linear transcripts	7/16 (44%)	2/2 (100%)
Reagent predicted to map to linear transcript from claimed circRNA host gene	6/7 (86%)	0/0 (0%)
Reagent predicted to map to claimed circRNA BSJ but also shows ≥ 17 nucleotides of identity to linear transcript	1/7 (14%)	2/2 (100%)
Claimed circRNA transcript ID does not map to the host gene described in study	2/16 (13%)	0/2 (0%)
Claimed circRNA targeting reagents predicted to be non-targeting in human	1/17 (6%)	4/6 (67%)
Proportion (percentage) of wrongly identified circRNA targeting reagents according to reagent type		
Single probes	9/17 (53%)	6/6 (100%)
PCR primers	8/17 (47%)	0/6 (0%)
Proportion (percentage) claimed circRNA targeting reagents that were NV	17/512 (3.3%)	6/97 (6%)
Study did not specify claimed circRNA target or provide BSJ sequence	17/17 (100%)	2/6 (33%)
Reagent claimed to target <i>circGAPDH</i> but match not confirmed using CircPRIMER	10/17 (59%)	2/2 (100%)
Study did not clearly define reagent as targeting circular or linear transcript from claimed host gene	0/17 (0%)	4/6 (67%)

2.3.1.2 Problematic *Molecular Cancer* papers with circRNA targeting reagents

Overall, 25 and 36 nucleotide sequence reagents were incorrectly identified in 3 and 13 *Molecular Cancer* papers in 2018 and 2020, respectively, representing 30% (3/10) and 43% (13/30) of original papers with circRNA targeting reagents published in *Molecular Cancer* in 2018 and 2020. The median number of incorrect sequence reagents per paper across the 16 problematic papers was 3 (range: 1-11) (Table 2.3). Of these 16 problematic papers, 56% (9/16) described wrongly identified circRNA targeting reagents. Just over half (5/9, 56%) *Molecular Cancer* papers with wrongly identified circRNA targeting reagents also contained wrongly identified nucleotide sequences claimed to target protein-coding genes and/or microRNAs (Supplementary Tables 1.1-1.2). The median number of incorrect circRNA targeting reagents per paper was 2 (range: 1-4).

The 9 problematic papers describing wrongly identified circRNA targeting reagents analysed a single cancer type, and most (8/9, 89%) mentioned a particular circRNA in their title (Supplementary Table 1.2). These 9 papers described experiments across 7 cancer types, such as hepatocellular carcinoma (2/9) and colorectal cancer (2/9) (Supplementary Table 1.2). Two problematic papers (PMID 32503552, 30470262) claimed in the title to study circRNA as a “sponge”, and two papers (PMID 32430013, 32487167) described circRNA to act via a gene “axis” (Supplementary Table 1.2). Some problematic papers claimed in their titles to study circRNA in the context of resistance to immunotherapy (PMID 32430013, 32593303), chemoresistance (PMID

32005118), or as a novel therapeutic target (PMID 31973707) (Supplementary Table 1.2).

2.3.1.3 Problematic *Oncogene* Papers with circRNA targeting reagents

Of the 42 *Oncogene* papers published in 2020 that referred to either miRNA and/or circRNA in their titles, four papers described one or more circRNA targeting reagents (Figure 2.3). The median number of nucleotide sequence reagents per paper with circRNA targeting reagents was 42 (range: 7-71) (Table 2.3, Figure 2.4A). Of the 162 nucleotide sequence reagents that were verified, 58% (94/162) were claimed to target circRNAs (Table 2.4, Figure 2.4B). The median number of circRNA targeting reagents per paper was 15 (range: 2-62) (Figure 2.4C, Table 2.4).

Overall, 4.3% (7/162) nucleotide sequences in three *Oncogene* papers with circRNA targeting reagents were wrongly identified (Table 2.3). Six (6/7, 86%) wrongly identified reagents were single-sequence probes (Table 2.3) claimed to target circRNA described in two papers (Table 2.4, Supplementary Tables 1.1, 1.2). The third paper described a single wrongly identified RT-PCR primer claimed to target a miRNA. One problematic paper (PMID 33122825) studied circRNA in nasopharyngeal carcinoma and described two circRNA targeting single probes (2/6, 33%) that were predicted to match the claimed BSJ but also target linear transcripts from the host gene (Table 2.4, Supplementary Tables 1.1, 1.2). The other problematic *Oncogene* paper (PMID 31705065) studied circRNA as regulators of a gene “axis” in bladder cancer and

described 4 single-sequence circRNA targeting probes that were verified as non-targeting in humans (Table 2.4, Supplementary Tables 1.1, 1.2).

2.3.1.4 Non-verifiable nucleotide sequence reagents in *Molecular Cancer* and *Oncogene* papers describing circRNA targeting reagents

Eight *Molecular Cancer* papers described 17 NV reagents that were claimed to target human circRNAs (Table 2.4). Reagent identities could not be verified either because a specific transcript identifier was not provided for the claimed circRNA, or insufficient sequence information was provided on the BSJ (Table 2.4). The most frequently claimed target was *circGAPDH* (59%, 10/17) (Table 2.4, Supplementary Table 1.3). Most (16/17, 94%) NV reagents were RT-PCR primers, with the remaining reagent being a single sequence probe (Supplementary Table 1.3). Of the 8 *Molecular Cancer* papers that described NV reagents, three papers also described wrongly identified nucleotide sequence reagents, where one paper (PMID 30470262) also described wrongly identified circRNA targeting reagents (Supplementary Table 1.3).

Two 2020 *Oncogene* papers (PMID 31705065 and 31570791) described 6 circRNA targeting reagents that were NV (Table 2.4). Reagent identities could not be verified because it was difficult to determine whether reagents were claimed to target circular or linear transcripts (4/6) or because the specific transcript identifier was not provided for the claimed circRNA (*circGAPDH*, 2/6) (Table 2.4). Most (4/6) NV reagents were single probes (Supplementary Table 1.3). Both *Oncogene* papers with NV reagents also described wrongly identified nucleotide sequence reagents, where one paper

(PMID 31705065) also described incorrect circRNA targeting sequence reagents (Supplementary Table 1.2, 1.3).

2.3.1.5 Countries of origin and institutional affiliations of problematic *Molecular Cancer* and *Oncogene* papers with circRNA targeting reagents

All 16 problematic *Molecular Cancer* papers featuring circRNA targeting reagents were authored by teams where the majority of authors were from China, and most (14/16, 88%) papers were also affiliated with hospitals (Table 2.5). The three *Oncogene* papers with incorrect nucleotide sequences were also authored by teams in China, where 2 papers (PMID 33122825, 31705065) were also affiliated with hospitals (Table 2.5, Supplementary Table 1.2).

Table 2.5. Demographics of *Molecular Cancer* and *Oncogene* papers describing wrongly identified nucleotide sequence reagents.

	Molecular Cancer	<i>Oncogene</i>
Papers with circRNA targeting reagents	40	4
Proportion (percentage) of screened papers with wrongly identified nucleotide sequence reagents	16/40 (40%)	3/4 (75%)
Author teams predominantly from China	16/16 (100%)	3/3 (100%)
Authors teams where majority were affiliated with hospitals	14/16 (88%)	2/3 (67%)

2.3.1.6 Citations, post-publication commentary/corrections of *Molecular Cancer* and *Oncogene* papers with wrongly identified nucleotide sequences.

The problematic *Molecular Cancer* papers that described circRNA targeting reagents were collectively cited 619 times (n=3, 2018 papers) and 2,338 times (n=13, 2020 papers) according to Google Scholar as of 07 September 2024. Most (5/8) 2020 papers with wrongly identified circRNA targeting reagents had accrued at least 150 citations, where two papers (PMID 32838810, 32593303) had accrued at least 250 citations (Figure 2.5, Supplementary Table 1.2). One 2018 *Molecular Cancer* paper (PMID 30470262) that described incorrect circRNA targeting reagents was cited 293 times (Figure 2.5, Supplementary Table 1.2). The two 2020 *Oncogene* papers with wrongly identified circRNA targeting reagents (PMID 33122825 and 31705065) had been cited 63 and 108 times, respectively (Figure 2.5)

One quarter (4/16) of problematic *Molecular Cancer* papers describing circRNA targeting reagents received publisher corrections, and half of these problematic papers (8/16) had received post-publication comments on PubPeer as of 01 April 2023 (Table 2.6). All corrections (5/5) and most PubPeer comments (6/8) cited concerns about image integrity (Table 2.6). One *Oncogene* paper received a PubPeer comment concerning image integrity that was addressed via a published correction (PMID 31705065, Supplementary Table 1.2).

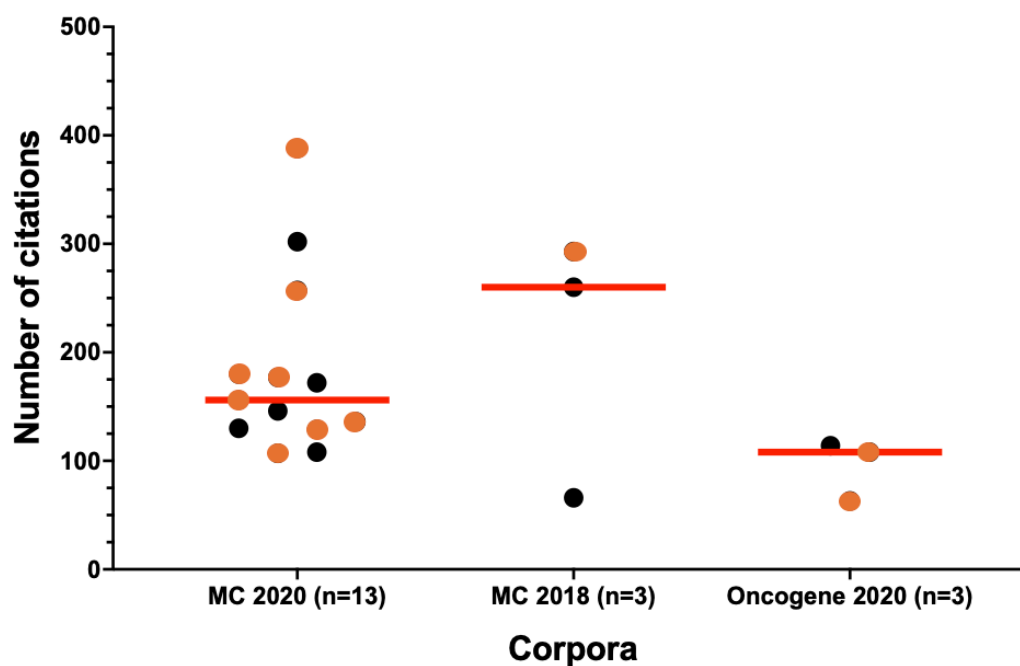


Figure 2.5. Number of Google Scholar citations (Y-axis) of *Molecular Cancer* (MC) and *Oncogene* papers with wrongly identified nucleotide sequence reagents according to journal and publication year (Y-axis). Individual citation numbers are shown as dots, where orange represents papers with incorrect circRNA targeting reagents, and black represents papers with wrongly identified nucleotide sequence reagents that were not claimed to target circRNA. Red bars represent median numbers of citations per corpus. Numbers of MC or *Oncogene* papers with wrongly identified nucleotide sequence reagents per year are shown below the X-axis.

Two *Molecular Cancer* papers (PMID 30470262 and 31973707) received PubPeer comments by anonymous posters citing concerns over the identities of circRNA targeting reagents, which we also identified in the present study. As of April 2023, one of these papers (PMID 30470262) had a published correction, providing new sequences for the circRNA targeting reagents that were verified to be correctly identified. However, other errors persisted in the correction notice (PMID 33126881),

as we had also identified a reverse RT-PCR primer sequence claimed to target a miRNA but was predicted to be a universal primer (Supplementary Tables 4.1 and 4.2, Chapter 3, Section 3.3.2) (Pathmendra et al., 2024). One *Molecular Cancer* paper with wrongly identified circRNA targeting reagents (PMID 32503552) was retracted on 20 March 2023, citing image concerns and queried methodology that had been flagged on PubPeer prior to the retraction. There was no mention of the wrongly identified circRNA targeting nucleotide sequence reagents that we identified in the retraction notice (PMID 36941569) (Supplementary Table 1.2).

Table 2.6. Post-publication corrections and commentary on *Molecular Cancer* and *Oncogene* papers describing wrongly identified nucleotide sequence reagents as of 01 April 2023.

	<i>Molecular Cancer</i>	<i>Oncogene</i>
Papers describing wrongly identified nucleotide reagent(s)	16	3
Published corrections	5/16 (31%)	1/3 (33%)
Image concerns	5/5 (100%)	1/1 (100%)
Wrongly identified nucleotide sequence reagents (including circRNA targeting reagents)	1/5 (20%)	0/1 (0%)
Retractions	1/16 (6%)	0/3 (0%)
Image integrity + methodological concerns	1/1 (100%)	0/0 (0%)
PubPeer Comments	8/16 (50%)	1/3 (33%)
Image concerns	6/8 (75%)	1/1 (100%)
Wrongly identified nucleotide sequence reagents (including circRNA targeting reagents)	2/8 (25%)	0/1 (0%)
Methodological concerns	3/8 (38%)	0/1 (0%)
PubPeer comments addressed in post-publication notice	6/8 (75%)	1/1 (100%)

2.3.2 Retracted circRNA papers in high impact factor journals corpus

We found 93 retractions of papers that mentioned human circRNA in their titles published from 2016 to 31 July 2023. The 93 retractions were published in 32 journals, where most (31/32, 97%) had a 2-year IF according to Clarivate Analytics. The median 2022 IF was 4.6 (range: 2.2-37.3, n=31 journals, Figure 2.6). A minority (13/93, 14%) of retracted papers were published in high IF journals, defined as having a 2022 IF \geq 7 (Figure 2.6) (Pathmendra et al., 2024). The high IF journals with the most retractions were *Journal of Experimental and Clinical Cancer Research* (2022 IF: 11.3, 23%, 3 retractions) and *Molecular Therapy and Nucleic Acids* (2022 IF: 8.8, 23%, 3 retractions) (Table 2.7). Two *Molecular Cancer* circRNA papers (PMID 32503552, 30621700) were retracted, of which one was published in 2020 and analysed in the previous section (PMID 32503552). Two *Oncogene* circRNA papers published in 2017 (PMID 28368401) and 2018 (PMID 30546088) were also retracted (Supplementary Table 2.1). Most (12/13) retracted papers studied a single cancer type, with the remaining paper (PMID 31900142) studying circRNA in the context of atherosclerosis (Supplementary Table 2.3). Some retracted papers referenced terms such as “axis” (n=5) or “sponge” (n=3) in their titles (Supplementary Table 2.1).

Of the 13 retracted circRNA papers in high IF journals, 12 papers reported at least one nucleotide sequence reagent claimed to target a non-modified human gene/transcript (Supplementary Tables 2.1, 2.2). Collectively, we verified 254 nucleotide sequence reagents from the 12 retracted circRNA papers in high IF journals. The median number of nucleotide sequence reagents analysed per paper was 23 (range: 2-55, n=12).

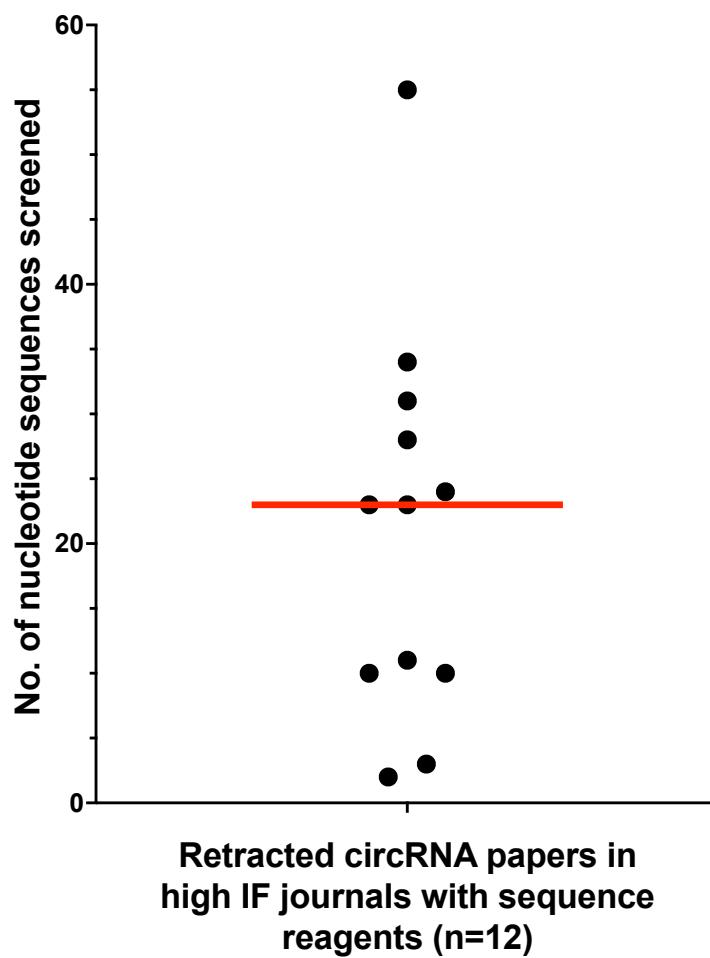


Figure 2.7. Number of nucleotide sequences analysed (Y-axis) per retracted circRNA paper in high IF journals (X-axis, n=number of retracted circRNA papers with sequences). Individual and median number of sequences analysed per paper are shown as black dots and red horizontal lines, respectively.

Table 2.7. Retracted circRNA papers

Total number of retracted circRNA papers (2016-31 st July 2023)	93
Number of journals (n=)	32
Journals with 2022 IF, proportion (percentage)	31/32 (97%)
Median 2022 IF (range)	4.6 (2.2-37.3)
Retracted circRNA papers in high IF (2022) journals (IF \geq 7)	13/93 (14%)
Proportion (percentage) authored by teams from China	13/13 (100%)
Proportion (%) affiliated with hospitals	12/13 (92%)
Proportion (percentage) according to journal	
<i>Journal of Experimental and Clinical Cancer Research</i> (2022 IF: 11.3)	3/13 (23%)
<i>Molecular Therapy and Nucleic acids</i> (2022 IF: 8.8)	3/13 (23%)
<i>Oncogene</i> (2022 IF: 8)	2/13 (15%)
<i>Cancer Letters</i> (2022 IF: 9.7)	2/13 (15%)
<i>Molecular Cancer</i> (2022 IF: 37.3)	2/13 (15%)
<i>Journal of Biomedical sciences</i> (2022 IF: 11)	1/13 (8%)
Retracted circRNA papers with nucleotide sequence reagents, proportion (percentage)	12/13 (92%)
Nucleotide sequence reagents analysed (n=)	254
Nucleotide sequence reagents analysed per paper, median (range)	23 (2-55)
Papers with wrongly identified nucleotide sequence reagents, proportion (percentage)	11/13 (85%)
Retracted high IF papers that include human cell lines	13/13 (100%)
Number of human cell lines analysed (n=)	52
Cell lines analysed per paper, median (range)	4 (1-8)
Papers with problematic cell line identifiers, proportion (percentage)	3/13 (23%)

2.3.2.1 Wrongly identified and non-verifiable nucleotide sequences in retracted circRNA papers in high impact factor journals

Of the 254 nucleotide sequences in retracted circRNA papers in high IF journals, 19% (49/254) were predicted to be wrongly identified (Table 2.8). The 49 wrongly identified nucleotide sequences were distributed across 11 retracted papers, with a median number of 2 incorrect sequences per paper (range: 1-20) (Figure 2.8A, Table 2.8). The 11 retracted papers with wrongly identified sequences were published by 6 journals (Supplementary Table 2.1).

Most wrongly identified nucleotide sequences (39/49, 80%) were claimed to target reagents that were predicted to target a different gene or genomic sequence (Table 2.8, Figure 2.8B). In contrast, fewer claimed targeting reagents were predicted to be non-targeting in human (20%, 10/49) (Table 2.7, Figure 2.8B). Most incorrect sequences (71%, 35/49) were claimed to target human circRNAs (Table 2.8, Figure 2.8B). In contrast, fewer incorrect reagents were claimed to target miRNAs or protein-coding genes (Table 2.8).

Two retracted circRNA papers (PMID 28368401 and 32194140) with wrongly identified nucleotide sequences also described NV circRNA targeting reagents (Supplementary Tables 2.1, 2.3). PMID 28368401 described 11 circRNA targeting siRNAs that were NV due to the use of ArrayStar circRNA identifiers that are not publicly available for external verification (Table 2.8, Supplementary Table 2.3). The other retracted paper, PMID 32194140, described one NV sequence where the BSJ sequence was not

provided, meaning that we were unable to identify the specific circRNA transcript (Table 2.8, Supplementary Table 2.3).

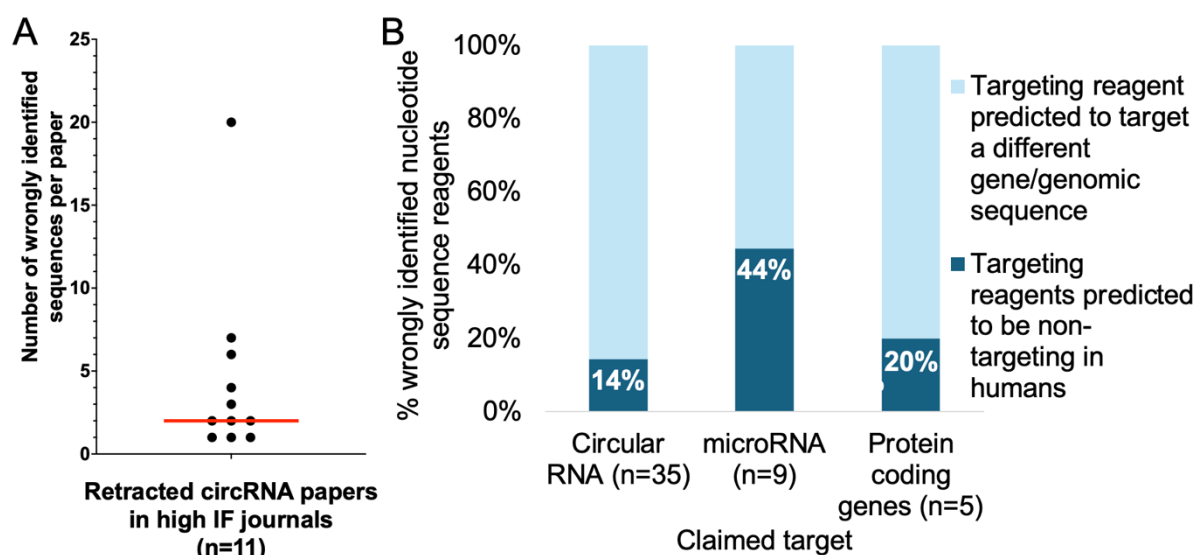


Figure 2.8. Summary of wrongly identified nucleotide sequences in retracted circRNA papers in high impact factor (IF) journals. A) Number of wrongly identified sequences per paper (Y-axis) in retracted circRNA papers (X-axis). Individual and median numbers of wrongly identified nucleotide sequence reagents are shown as black dots and a red horizontal line, respectively. B) Percentages of wrongly identified nucleotide sequence reagents (Y-axis) according to claimed identity (X-axis). Numbers of wrongly identified reagents are shown below the X-axis. Claimed targeting reagents predicted to target a different gene or genomic sequence are shown in light blue, claimed targeting reagents predicted to be non-targeting in humans are shown in dark blue.

Table 2.8. Wrongly identified and non-verifiable (NV) nucleotide sequence reagents in retracted circRNA papers in high-IF journals.

Nucleotide sequence reagents analysed (n=)	254
Proportion (percentage) of wrongly identified nucleotide sequence reagents	49/254 (19%)
Proportion (percentage) of wrongly identified reagents according to error types	
Claimed targeting reagents predicted to target a different human gene or genomic sequence	39/49 (80%)
Claimed targeting reagents predicted to be non-targeting in human	10/49 (20%)
Proportion (percentage) of wrongly identified reagents according to claimed identity	
circRNAs	35/49 (71%)
Claimed targeting reagents predicted to target a different human gene or circRNA	23/35 (66%)
Claimed to target circRNA but predicted to not discriminate between circular and linear host gene transcripts	7/35 (20%)
Claimed targeting reagents predicted to be non-targeting in human	5/35 (14%)
microRNA (including promoters)	9/49 (18%)
protein-coding genes (including promoters)	5/49 (10%)
Proportion (percentage) of wrongly identified nucleotide sequence reagents according to reagent type	
RT-PCR primers	41/49 (84%)
Single probes	8/49 (16%)
Number of wrongly identified reagents per retracted paper, median (range)	2 (1-20)
Proportion (percentage) of NV nucleotide sequence reagents	12/254 (4.7%)
Claimed circRNA identifier not listed on publicly available database	12/12 (100%)
Use of ArrayStar ID with no BSJ information	11/12 (92%)
Insufficient BSJ information	1/12 (8%)

2.3.2.2 Problematic cell lines in retracted circRNA papers in high impact factor journals

Of the 52 cell lines whose identities were manually verified in 13 retracted circRNA papers, 10% (6/52) were predicted to be problematic (Table 2.9). Most problematic cell lines (5/6) were recognised as contaminated cell lines, often by HeLa cells (SGC-7901, BGC-823, MGC803) or by another cell line of the same claimed cancer type (40%, 2/5, MKN-28, K1) (Table 2.9). One cell line, HepG2, was misclassified as a hepatocellular adenocarcinoma cell line (PMID 30546088) (Supplementary Table 2.4). Most problematic cell lines were claimed to be models of gastric cancer (4/6) (Table 2.9).

The six problematic cell lines were found in three (3/13) retracted circRNA papers (PMID 30546088, 33308284, 32059339) (Supplementary Table 2.1). One of these retracted papers (PMID 30546088) also described one wrongly identified nucleotide sequence reagent (Supplementary Table 2.1). The three retracted papers described experiments in a single cancer type and were authored by teams of authors affiliated with hospitals in China (Supplementary Table 2.1). The three retracted papers were published by the *Journal of Experimental and Clinical Cancer Research* (2022 IF: 11.3), *Molecular Therapy and Nucleic Acids* (2022 IF: 8.8), and *Oncogene* (2022 IF: 8) (Supplementary Table 2.1).

Table 2.9. Problematic cell lines in retracted circRNA papers published in high impact factor journals.

Number of cell lines analysed (n=)	52
Proportion (percentage) of problematic cell lines	6/52 (10%)
Problematic cell lines per paper, median (range)	1 (1-4)
Proportion (percentage) of problematic cell lines according to error type	
Contaminated cell lines	5/6 (83%)
HeLa contamination	3/5 (60%)
HeLa cell line as sole contaminant (SGC-7901, BGC-823)	2/3 (67%)
Partial contamination by HeLa and cell line of claimed identity forming a hybrid cell line (MGC803)	1/3 (33%)
Contamination by another cell line of same cancer type (MKN-28, K1)	2/5 (40%)
Misclassified cell lines (HepG2)	1/6 (17%)
Proportion (percentage) of problematic cell lines according to claimed identity	
Gastric cancer (MKN-28, SGC-7901, MGC-803, BGC-823)	4/6 (67%)
Hepatocellular carcinoma (HepG2)	1/6 (17%)
Papillary thyroid carcinoma (K1)	1/6 (17%)

2.3.2.3 Overview of the retraction notices and associated comments on PubPeer

Most (10/13) retracted circRNA papers in high IF journals cited concerns regarding image integrity, including duplications and manipulations of figures, as the reason for retraction (Table 2.10). Retraction notices for half of these retracted papers (5/10) also cited issues such as problematic ethics approval (PMID 30621700), methodological issues (PMID 32503552), potential authorship fraud (PMID 33614250), wrongly identified cell lines (PMID 33308284) or that an undeclared 'third party provided the images' (PMID 32928266) (Supplementary Table 2.1). The three retraction notices that did not cite image integrity concerns described issues with ethics approval (PMID 32430042), irreproducibility of results (PMID 32194140) and lack of confidence in the publication due to involvement of a 'revision agency' (PMID 32059339) (Supplementary Table 2.1). According to retraction notices, most retractions (6/10) were initiated by the editors in chief, where the authors either disagreed with or did not respond to the decision to retract the paper (Supplementary Table 2.1). Only one retraction notice stated that the concerns listed were initially reported on PubPeer (PMID 32193152, Supplementary Table 2.1).

Most (9/10) of the circRNA papers retracted due to image integrity concerns also received PubPeer comments describing image integrity concerns by anonymous posters prior to the retractions (Table 2.10, Supplementary Table 2.1). The median number of months between the first PubPeer comment and the subsequent retraction was 7 (range: 3-20) (Table 2.10). Just over half of the PubPeer comments (5/9) received responses from authors on PubPeer, where the authors declared their intent

to communicate with journal editors and seek an erratum. In one of these PubPeer threads associated with a retracted circRNA paper (PMID 32928266), the authors explained that a company had produced the images with integrity concerns. However, the anonymous poster noted this declaration conflicted with the authorship statement that the authors had made. Thus, the involvement of an undeclared third party was noted in the retraction notice as a key concern undermining confidence in the study's data.

Most (11/13, 85%) retracted circRNA papers in high IF journals described wrongly identified nucleotide sequence reagents that were not flagged in retraction notices (0/11) or PubPeer comments (0/11) (Table 2.10). Similarly, of the 3 papers describing the use of wrongly identified cell lines, none had PubPeer comments flagging problematic cell line use (Table 2.10). One paper (PMID 33308284) received a retraction notice that mentioned a wrongly identified cell line. The study authors claimed in the retraction notice (PMID 37101243) that four contaminated cell lines (MKN-28, SGC-7901, MGC-803, BGC-823) were used in validation experiments and were unlikely to have affected the conclusions.

Table 2.10. Summary of retractions and prior PubPeer comments on retracted circRNA papers in high-IF journals.

Number of retracted circRNA papers in high IF \geq 7	13
Proportion (percentage) of retracted circRNA papers with problematic cell lines	3/13 (23%)
Cell lines issue(s) described in retraction notice	1/3 (33%)
Cell lines issue(s) flagged on PubPeer	0/3 (0%)
Proportion (percentage) of retracted circRNA papers with wrongly identified nucleotide sequence reagents	11/13 (85%)
Wrongly identified nucleotide sequence(s) described in retraction notice	0/11 (0%)
Wrongly identified nucleotide sequence(s) flagged on PubPeer	0/11 (0%)
Proportion (percentage) of retracted papers according to retraction reason	
Image integrity concerns	10/13 (77%)
Problematic ethics approval	2/13 (15%)
Involvement of undeclared third party (revision agency, results provided by third party)	2/13 (15%)
Authorship fraud	1/13 (8%)
Methodological concerns	1/13 (8%)
Wrongly identified cell lines	1/13 (8%)
Unable to replicate/reproduce data	1/13 (8%)
Proportion (percentage) of papers with PubPeer comments before retraction	9/13 (69%)
PubPeer comments describing:	
Image integrity concerns	9/9 (100%)
Methodological concerns	1/9 (11%)
Involvement of undeclared third party (results provided by third-party)	1/9 (11%)
Number of months between first PubPeer comment and retraction, median (range)	7 (3-20)

2.3.3 circRNA papers published in high impact factor journals during 2022

We identified 5,567 papers published from 2001-2022 available via Web of Science with titles containing circRNA-related terms ("circular RNA*" OR "circRNA*" OR "hsa_circ*" OR "hsa-circ*" OR "hsacirc*" OR "circ* RNA*") (Figure 2.9A). Publication numbers remained below 100 papers per year until 2017 (Figure 2.9A). From 2016, there was a rapid increase in the number of circRNA papers, reaching over 1,000 in 2020, and peaking at 1,404 in 2021 (Figure 2.9A). These increases were primarily contributed by papers from China (Figure 2.9B). In 2022, 1,276 original circRNA papers were published across 475 journals, of which 98% (464/475) of journals were assigned an IF in 2022. The median IF of the 464 journals was 3.75 (range: 0.1-64.5), where 16% (74/464) of journals had an $IF \geq 7$.

Fifteen per cent (190/1,276) of all original 2022 circRNA papers were published across 74 journals with a high IF ($IF \geq 7$). Of these, 62% (118/190) papers were analysed as they described at least one nucleotide sequence reagent claimed to target a non-modified human gene or genomic sequence and/or described the use of at least one human cell line. Articles that were excluded were either i) bioinformatic studies with no experimental component (27/72, 38%), ii) circRNA studies in species other than human (26/72, 36%), typically in mice or rats (14/26, 54%), iii) reviews of circRNA research (10/72, 14%), iv) studies did not use sequence reagents or cell lines (4/72, 6%), v) studies that did not disclose the identities of the nucleotide sequences or cell lines (3/72, 4.2%), or vi) studies of circulating RNA (1/72, 1.4%) which is distinct from

circRNA or vii) studies only used sequence reagents claimed to target modified gene targets (1/72, 1.4%) (Supplementary Table 3.1A).

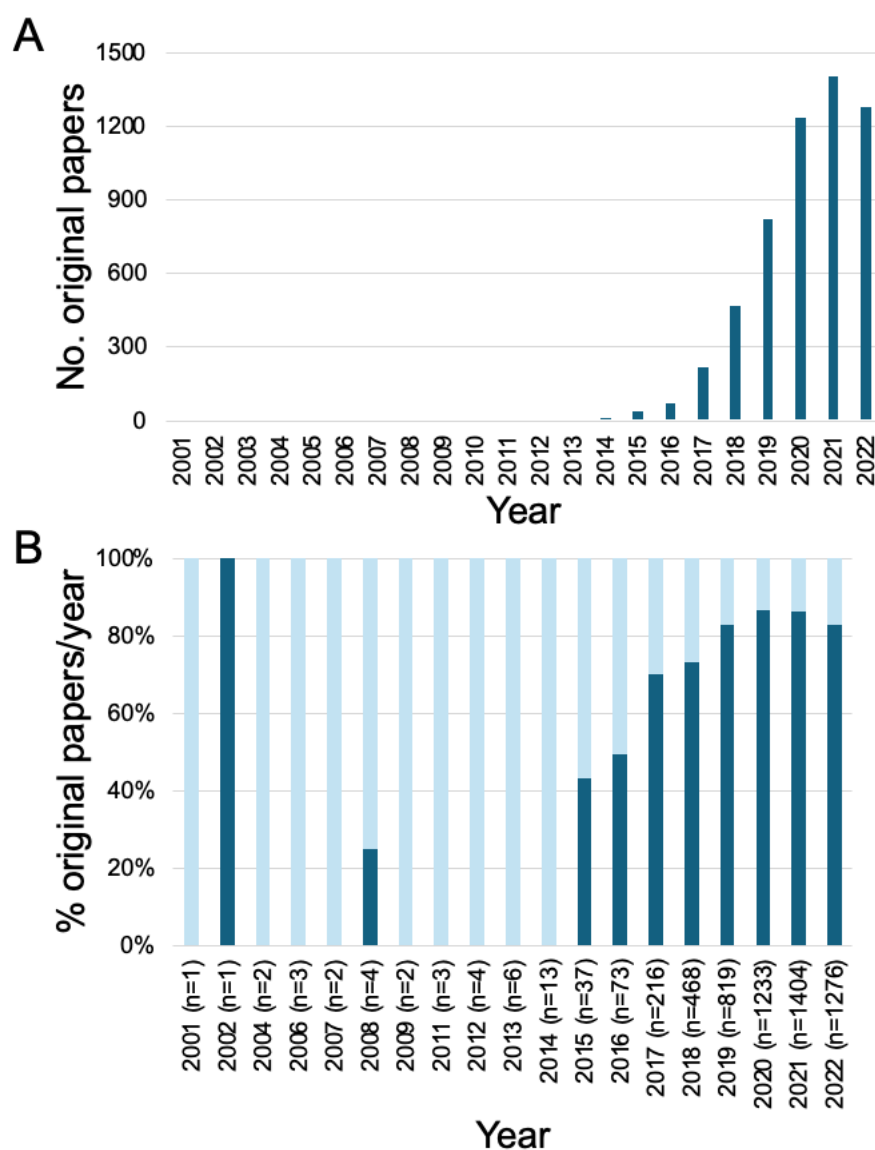


Figure 2.9. Summary of original circRNA papers. A) Number of original circRNA papers (Y-axis) published from 2001 to 2022 according to publication year (X-axis). B) Percentage of original circRNA papers (Y-axis) published per year (X-axis). Numbers of original papers are shown below the X-axis. Proportions of papers with all authors located in China are shown in dark blue, papers with at least one author from a country other than China are shown in light blue.

Collectively, 113 circRNA papers (113/118, 96%) reported 3,370 nucleotide sequence reagents, and 90 papers (90/118, 76%) reported 392 human cell lines. Papers described a median of 22 nucleotide sequences per paper (range: 1-154) and four cell lines per paper (range: 1-10). Most nucleotide sequence reagents were claimed to target protein-coding genes (1,601/3,370, 48%) or circRNA (1,283/3,370, 38%) (Figure 2.10). The 1,283 claimed circRNA targeting reagents (Supplementary Table 3.2) were distributed across 91% (107/118) of the analysed papers. The median number of circRNA reagents per paper was 8 (range: 2-84). Of the 113 circRNA papers, 38 papers (38/113, 34%) described nucleotide sequence reagents where at least 50% were claimed circRNA targeting reagents (Figure 2.11).

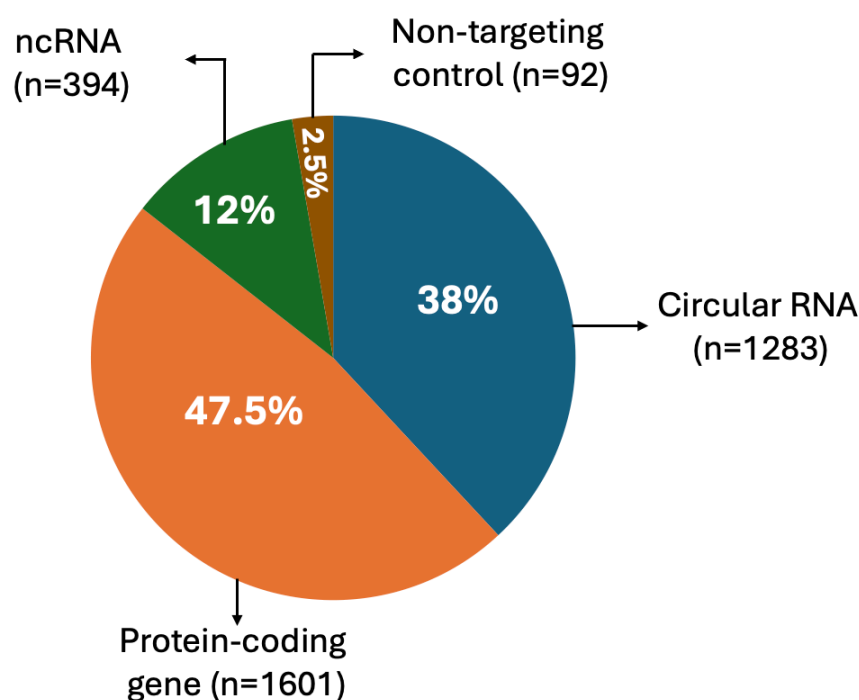


Figure 2.10. Pie chart showing proportions of nucleotide sequence reagents according to the claimed target category. “Non-targeting control” refers to reagents claimed to not target any human gene or transcript. Percentages are shown in white text, claimed identity and n = number of verified reagents indicated by arrows.

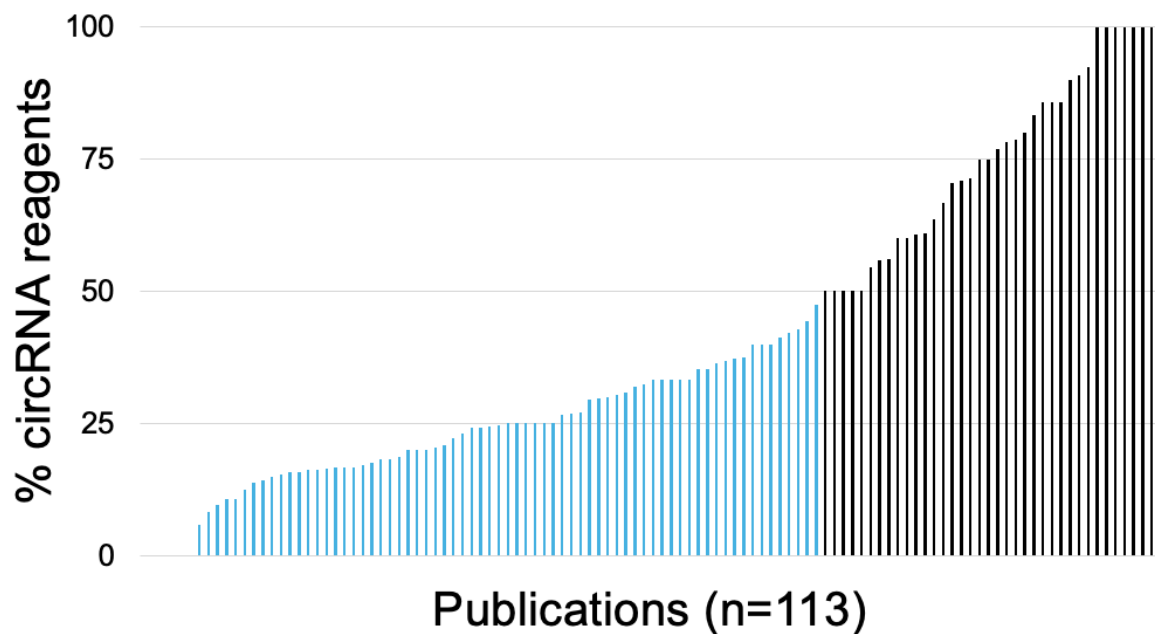


Figure 2.11. Percentage of circRNA reagents (Y-axis) per paper (X-axis). Each line represents a single paper; papers with $\geq 50\%$ nucleotide sequence reagents that were claimed to target human circRNAs are shown in black, and other papers are shown in blue.

2.3.3.1 Wrongly identified sequences in 2022 circRNA papers in high impact factor journals

Of the verified 3,370 nucleotide sequences, 201 (6.0%) nucleotide sequences were predicted to be wrongly identified. Most wrongly identified sequences were claimed targeting reagents that were predicted to target a different human gene or genomic sequence (117/201, 58%), followed by targeting reagents predicted to be non-targeting in human (81/201, 40%) (Table 2.11). Few reagents (3/201, 1.5%) were non-targeting controls that were predicted to target a human gene. Most wrongly identified targeting reagents were PCR primers (Figure 2.12A). Most incorrect sequence reagents were either claimed to target protein-coding genes (88/201, 44%) or circRNAs (71/201, 35%) (Table 2.11). Most incorrect reagents that were claimed to target protein-coding genes were RT-PCR primers (65/88, 74%) (Figure 2.12B).

Of the 1,283 claimed circRNA targeting reagents, 5.5% (71/1,283) were wrongly identified, with most being single probes (45/71, 63%) (Figure 2.12B). Most wrongly identified circRNA reagents (52/71, 73%) were claimed targeting reagents predicted to target a different human gene/genomic sequence, where most (37/52, 71%) were predicted not to discriminate between circular and linear transcripts from the claimed host gene (Table 2.12). Most incorrect non-discriminative circRNA reagents were predicted to match sequences common to the circRNA and linear transcript (24/37, 65%), including claimed divergent RT-PCR primers that were predicted to function as convergent primers (8/24, 33%) (Table 2.12). Some (13/37, 35%) reagents were predicted to map to the claimed BSJ but also showed ≥ 17 nucleotides of identity to a linear transcript (Table 2.12).

Other incorrect circRNA targeting reagents were predicted to target a different gene (14/52, 27%), with similar proportions predicted to target a different circRNA (6/14, 43%) or a different human gene (5/14, 36%) (Table 2.12). Several of these incorrect circRNA targeting reagents (3/14, 21%) were predicted to target linear transcripts from the host gene that were not included in the claimed circRNA transcript (Table 2.12). In contrast, few incorrect circRNA reagents were predicted to be non-targeting in human (19/71, 27%), with most being single probes (12/19, 63%) (Table 2.12, Supplementary Table 3.2). Five incorrect circRNA reagents (7.0%) showed insufficient identity to the claimed BSJ, where most (3/5, 60%) were also predicted to be non-targeting (Supplementary Table 3.2).

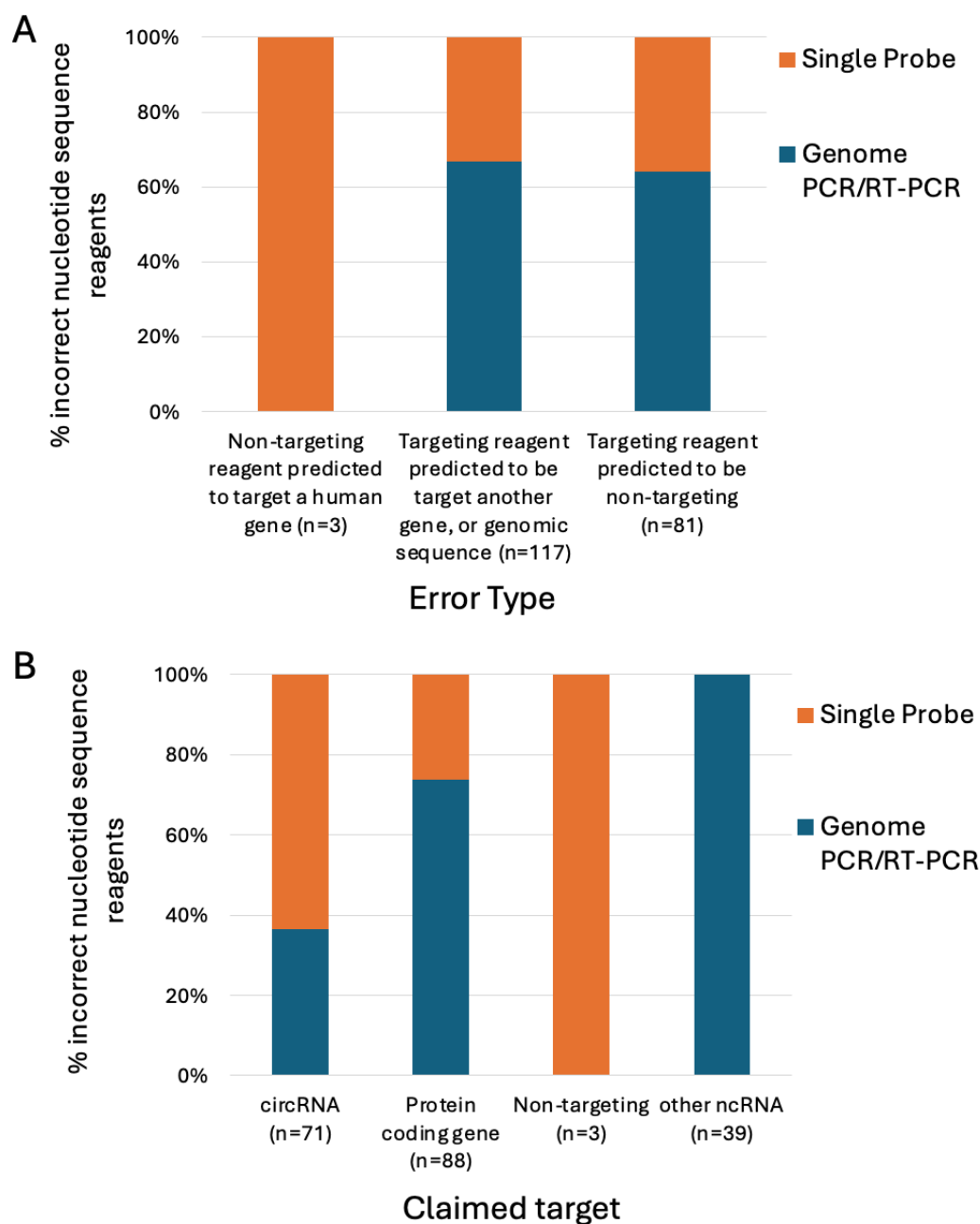


Figure 2.12. Wrongly identified nucleotide sequence reagents in 2022 circRNA papers in high-IF journals. PCR primers (including RT-PCR and genome PCR) are shown in blue; single reagents are shown in orange. Percentage of wrongly identified nucleotide sequences according to (A) error type (X-axis) or (B) claimed target (X-axis). (A, B) N values below X axes show the numbers of wrongly identified nucleotide sequence reagents.

Table 2.11. Wrongly identified nucleotide sequence reagents in 2022 circRNA papers published in high IF journals

Nucleotide sequence reagents analysed, n=	3,370
Proportion (percentage) of wrongly identified nucleotide sequence reagents	201/3,370 (6.0%)
Papers with verifiable nucleotide sequence reagents, n=	113
Proportion (percentage) of papers describing wrongly identified nucleotide sequence reagents	52/113 (46%)
Wrongly identified nucleotide sequences per paper, median (range)	2 (1-32)
Proportion (percentage) according to error type	
Claimed targeting reagents predicted to target a different human gene/genomic sequence	117/201 (58%)
Claimed targeting reagents predicted to be non-targeting in human	81/201 (40%)
Claimed non-targeting reagents predicted to target a human gene	3/201 (1.5%)
Proportion (percentage) according to claimed identity	
Protein coding genes (including promoters)	88/201 (44%)
CircRNA	71/201 (35%)
Other ncRNAs (e.g. microRNAs, lncRNAs)	39/201 (19%)
Non-targeting	3/201 (1.5%)
Proportion (percentage) according to reagent types:	
PCR primers	130/201 (65%)
Single reagents (siRNA, shRNA, other oligonucleotide probes)	71/201 (35%)

Table 2.12. Wrongly identified circRNA targeting reagents in 2022 papers in high IF journals

Nucleotide sequence reagents analysed, n=	3370
Proportion (percentage) claimed circRNA targeting reagents	1,283/3,370 (38%)
Proportion (percentage) wrongly identified circRNA reagents	71/1,283 (5.5%)
Proportion (percentage) of wrongly identified circRNA targeting reagents according to error type	
Claimed targeting reagents predicted to target a different human gene/genomic sequence	52/71 (73%)
Predicted to not discriminate between circular and linear transcripts from the claimed host gene	37/52 (71%)
Predicted to target sequence shared by circRNA and linear transcript (does not amplify claimed BSJ)	24/37 (65%)
Claimed divergent RT-PCR primers predicted to function as convergent primers (do not amplify claimed BSJ)	8/24 (33%)
Predicted to map across BSJ yet also target linear transcript	13/37 (35%)
Predicted to target other gene/genomic sequence	14/52 (27%)
Predicted to target a different circRNA	6/14 (43%)
Predicted to target a different circRNA isoform from claimed host gene	2/6 (33%)
Predicted to target a different gene	5/14 (36%)
Reagent showed insufficient match to claimed BSJ	1/5 (20%)
Predicted to target a linear transcript from claimed host gene not shared by claimed circRNA	3/14 (21%)
Duplicated primers (identical sequences provided as forward and reverse RT-PCR primers)	1/52 (1.9%)
Claimed targeting reagents predicted to be non-targeting in human	19/71 (27%)
Claimed circRNA targeting reagents showed less than accepted homology across the BSJ	3/19 (16%)

2.3.3.2 circRNA papers in high impact factor journals published in 2022 with wrongly identified nucleotide sequences

The 201 wrongly identified nucleotide sequences were distributed across 46% (52/113) circRNA papers that described nucleotide sequences, where the median number of wrongly identified nucleotide sequences per paper was 2 (range: 1-32) (Table 2.11). We found a statistically significant weak positive correlation between the numbers of nucleotide sequences screened and the numbers of wrongly identified sequences per paper (Spearman Rho = 0.2807, 95% CI: 0.0002216 to 0.5203, $p=0.0438$, $n=52$) (Figure 2.13). Half (26/52, 50%) of the incorrect circRNA papers described at least one wrongly identified circRNA targeting reagent, where 13 (13/26, 50%) papers only described wrongly identified circRNA targeting reagents (Supplementary Tables 3.2, 3.3).

The 52 circRNA papers with wrongly identified nucleotide sequences were published across 28 high IF journals, with a median IF of 9 (range: 7-39.3), where approximately half of these journals (14/28, 50%) were published by Springer Nature. More than half of the papers were collectively published across 6 journals: *Cell Death & Disease* ($n=8$, 2022 IF: 9), *Molecular Cancer* ($n=7$, 2022 IF: 37.3), *Cell Death and Discovery* ($n=7$, 2022 IF: 7), *Molecular Therapy, Nucleic Acids* ($n=3$, 2022 IF: 8.8), *Journal of Translational Medicine* ($n=3$, 2022 IF: 7.4) and *Nature Communications* ($n=2$, 2022 IF: 16.6) (Table 2.12). Most incorrect papers (46/52, 88%) were published open access (Supplementary Table 3.3). Most (48/52, 92%) incorrect circRNA papers described experiments in 13 diseases, typically human cancers (33/48, 69%) (Supplementary Table 3.5). Four incorrect papers studied circRNAs in the context of general biological

function (Supplementary Table 3.5). Some incorrect papers claimed to study circRNAs in the context of a “gene axis” (12/52, 23%), or as sponges of miRNA (7/52, 13%) (Supplementary Table 3.3).

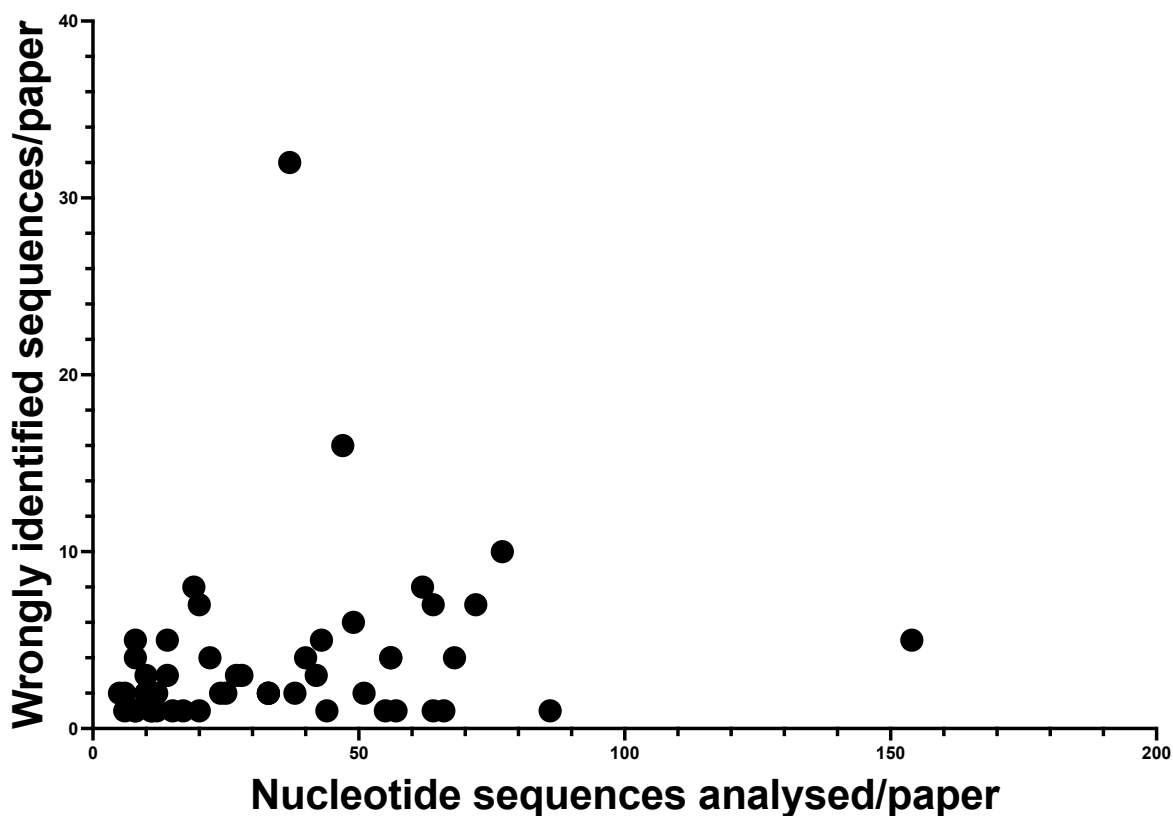


Figure 2.13. Number of wrongly identified nucleotide sequences per paper (Y-axis) versus the total number of sequence reagents analysed per paper (X-axis) in incorrect 2022 circRNA papers in high impact factor journals. Individual papers with wrongly identified nucleotide sequences are shown as black dots.

Table 2.13. Journals that published circRNA papers with wrongly identified sequences

Journal (asterisked journals are open access)	2022 Journal Impact Factor	Papers screened (n=113)	Proportion of screened papers with wrongly identified nucleotide sequences
Springer Nature			
<i>Cell Death & Disease</i> *	9	11	8/11 (73%)
<i>Molecular Cancer</i> *	37.3	12	7/12 (58%)
<i>Cell Death Discovery</i> *	7	7	7/7 (100%)
<i>Nature Communications</i> *	16.6	2	2/2 (100%)
<i>Journal of Translational Medicine</i> *	7.4	6	3/6 (50%)
<i>Basic Research in Cardiology</i>	8.5	1	1/1 (100%)
<i>Bone Research</i> *	12.7	1	1/1 (100%)
<i>Breast Cancer Research</i> *	7.4	1	1/1 (100%)
<i>Cellular and Molecular Life Sciences</i>	8	1	1/1 (100%)
<i>Experimental & Molecular Medicine</i> *	12.8	2	1/2 (50%)
<i>Genome Biology</i> *	12.3	2	1/2 (50%)
<i>Journal of Experimental & Clinical Cancer Research</i> *	11.3	2	1/2 (50%)
<i>Molecular Psychiatry</i>	11	2	1/2 (50%)
<i>Oncogene</i>	8	1	1/1 (100%)
Elsevier			
<i>Molecular Therapy Nucleic Acids</i> *	8.8	9	3/9 (33%)
<i>Cancer Letters</i>	9.7	1	1/1 (100%)
<i>Molecular Therapy</i> *	12.4	2	1/2 (50%)
<i>Thrombosis Research</i>	7.5	1	1/1 (100%)
American Association of Cancer Research			
<i>Cancer Research</i>	11.2	1	1/1 (100%)
Wiley			
<i>Cell Proliferation</i> *	8.5	2	1/2 (50%)
<i>Clinical and translational medicine</i> *	10.6	4	1/4 (25%)
<i>Journal of Medical Virology</i>	12.7	2	1/2 (50%)
<i>Journal of Pineal Research</i>	10.3	1	1/1 (100%)
Oxford University Press			
<i>Clinical Chemistry</i>	9.3	1	1/1 (100%)
<i>European Heart Journal</i>	39.3	1	1/1 (100%)
Taylor & Francis			
<i>Emerging Microbes & Infections</i> *	13.2	1	1/1 (100%)
Ivyspring International Publisher			
<i>International Journal of Biological Sciences</i> *	8.2	2	1/2 (50%)

2.3.3.3 Non-verifiable nucleotide sequence reagents in 2022 circRNA papers in high impact factor journals

As we had identified NV circRNA targeting reagents in earlier *Molecular Cancer* and *Oncogene* papers (Section 2.3.1.4, Table 2.4) and in retracted circRNA papers (Section 2.3.2.1, Table 2.8), we performed similar analyses of 2022 circRNA papers in high-IF journals. We found that 21% (24/113) of 2022 circRNA papers described 86 (86/3,370, 2.6%) NV reagents, with a median of 2 (range: 1-14) NV sequence reagents described per paper (Table 2.14). Nine papers (9/24, 38%) with NV sequences also described at least one wrongly identified nucleotide sequence reagent (Table 2.14). Most NV sequence reagents were RT-PCR primers (64/86, 74%), with the remaining NV reagents being single sequence probes (Table 2.14).

Almost all (84/86, 98%) NV sequences were claimed to target human circRNAs (Table 2.14) and provided generic circRNA identifiers with insufficient information about the BSJ, such that we could not identify a specific transcript using circATLAS or circBASE. These included non-specific identifiers (41/84, 49%) that used the host gene name (33/41, 80%), where 30% (10/33) of reagents with this identifier format were claimed to target *circGAPDH*, or NV circRNA identifiers that appeared to be unique to the paper (8/41, 20%) (Table 2.14, Supplementary Table 3.6). Some NV reagents used ArrayStar circRNA identifiers (32/84, 38%) or identifiers that resembled ArrayStar identifiers (ID) (11/82, 13%), which could not be independently verified (Table 2.14). Two NV sequences were not claimed to target circRNAs. One RT-PCR primer claimed to target *BACH1* could not be searched via BLAT or Blastn due to disclosing seven nucleotides (PMID 35918398). The other paper (PMID 35821230) described a reagent labelled

“URP” without explanation, where this could refer to universal reverse primer (Table 2.14, Supplementary Table 3.6).

Table 2.14. Non-verifiable (NV) nucleotide sequence reagents in 2022 circRNA papers published in high-IF journals

Nucleotide sequence reagents analysed, n=	3,370
Proportion (percentage) NV sequence reagents	86/3,370 (2.6%)
NV sequences per paper, median (range)	2 (1-14)
Proportion (percentage) of NV reagents that were claimed to target circRNAs	84/86 (98%)
Claimed circRNA identity could not be independently verified on circATLAS or circBASE, authors did not provide or reference the complete circRNA sequence	41/84 (49%)
No reference to a specific circRNA transcript	33/41 (80%)
Claimed circRNA target referred by a unique identifier	8/41 (20%)
Use of ArrayStar ID with no information, numerical component of circRNA ID did not correspond to any circBASE ID	32/84 (38%)
Claimed circRNA ID resembles ArrayStar ID, but no reference to ArrayStar in methods	11/84 (13%)
Other NV sequence reagents not claimed to target circRNAs	2/86 (2.3%)
Short nucleotide sequence (n=7 nucleotides)	1/2 (50%)
Unclear annotation	1/2 (50%)
Proportion (percentage) of NV reagents according to reagent type	
RT-PCR primers	64/86 (74%)
Single sequence probes (sgRNA, shRNA, siRNA, other oligonucleotide probes)	22/86 (26%)
Papers with verifiable nucleotide sequence reagents, n=	113
Proportion (percentage) papers that described NV sequences	24/113 (21%)
Proportion (percentage) that also described wrongly identified nucleotide sequences	9/24 (38%)

2.3.3.4 circRNA targeting reagents employed in FISH, RNA Pull-down, and Northern blot assays

2.3.3.4.1 (Fluorescence) In Situ Hybridisation (FISH/ISH) probes

Across 26 circRNA papers, we found 27 FISH/ISH single probes claimed to target circRNAs that were predicted to map to the claimed BSJ (Figure 2.14). Approximately half (15/27, 56%) of these probes were reported in papers that also described wrongly identified nucleotide sequence reagents (Supplementary Table 3.7). None of the circRNA targeting FISH/ISH probes satisfied the ideal targeting criteria of 22-24nt complementarity to either side of the BSJ (Zirkel and Papantonis, 2018) (Table 2.1, Figure 2.14). Some (10/27, 37%) FISH/ISH probes showed equivalent numbers of identity matches on either side of the BSJ (Figure 2.14). A similar proportion (7/27, 26%) unevenly matched the claimed BSJ, where the lengths of identity matches differed by at least five nucleotides between the 5' and 3' sides of the BSJ (Figure 2.14, Supplementary Table 3.7).

2.3.3.4.2 Northern blot probes

Two circRNA papers (PMID 34976440, 35153295) reported oligonucleotide probes used in Northern blot assays. One paper (PMID 34976440) described a probe of 331 nt length that showed 110 nt and 123 nt of identity to the 5' and 3' sides of the claimed BSJ, respectively. The other described (PMID 35153295) a shorter probe of 25 nt that showed 9 and 16 nucleotides of identity to the 5' and 3' sides of the claimed BSJ.

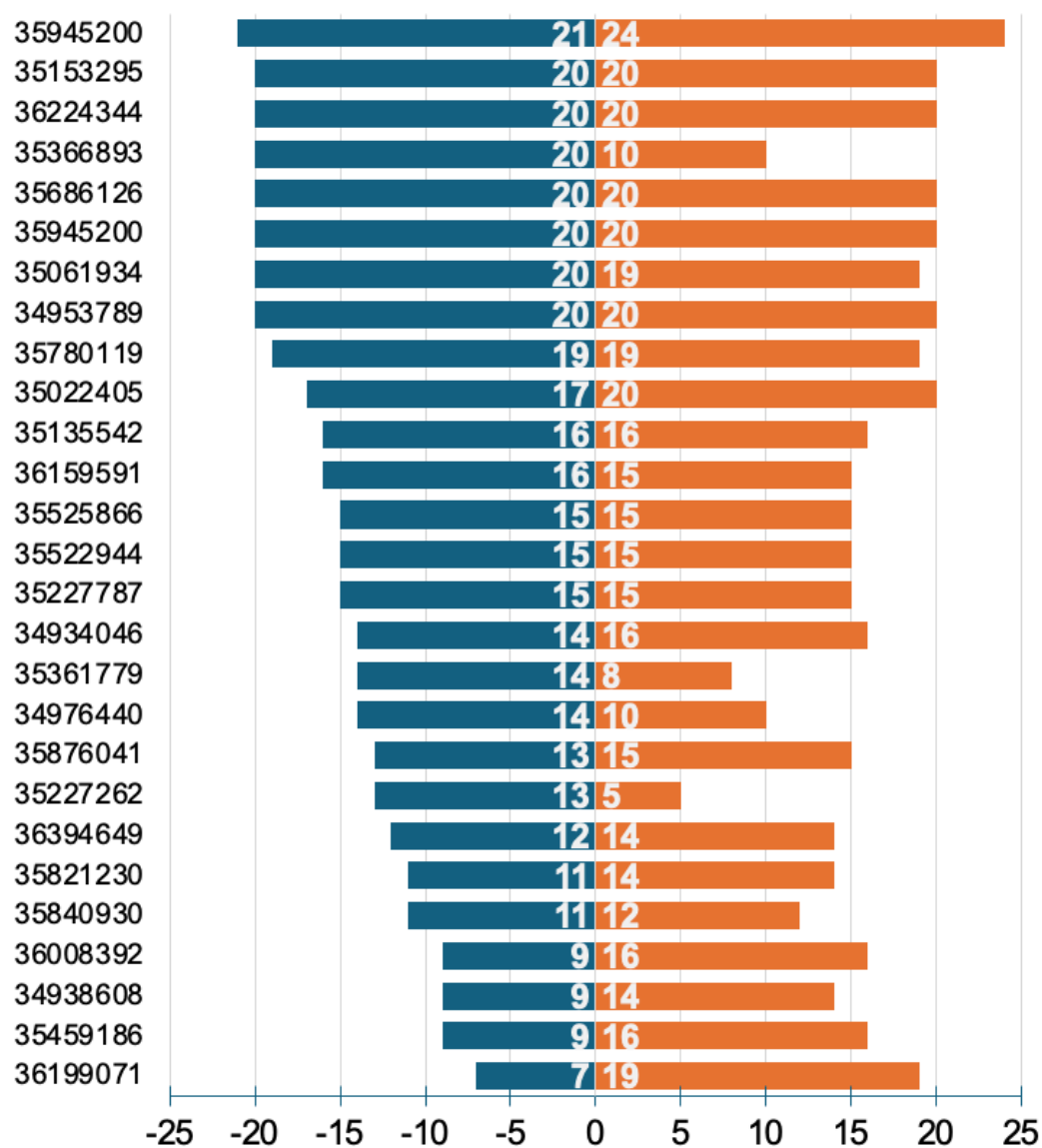


Figure 2.14. Summary of Fluorescence and/or In Situ Hybridisation (FISH/ISH) probes according to the extent of sequence identity across the BSJ of the claimed circRNA target. Probes labelled by PMID (left) and mapped across the claimed BSJ (X-axis). Sequences 5' (negative numbers, X-axis) and 3' (positive numbers) are shown on either side of the BSJ (0 position). Matches to the 5'/3' side of the BSJ are shown in dark blue/orange, respectively, with match lengths shown in white.

2.3.3.4.3 RNA-pull down probes

Across 23 circRNA papers, we found 31 RNA-pull down probes claimed to target circRNAs that were predicted to show identity to either side of the claimed BSJ (Figure 2.15). Approximately two-thirds (15/23, 65%) of papers with these probes also described wrongly identified nucleotide sequence reagents (Supplementary Table 3.7). Seven RNA-pulldown probes (23%) satisfied the targeting criteria (Das et al. 2021; Gabryelska et al. 2024) (Table 2.1), where probes were 20-40 nt in length and showed equivalent matches to both sides of the claimed BSJ (Figure 2.15). Five RNA-pulldown probes (5/31, 16%) were greater than 40nt in length but showed similar matches (differing by 1-3 nt) to the 5' and 3' sides of claimed BSJ (Figure 2.15). One such probe (PMID 35840930) showed 338 nt of identity across the BSJ with similar matches across each side (PMID 35840930, Figure 2.15).

As the minimal length for a circRNA targeting RNA-pull down probe is 20nt, with equivalent matches to either side of the BSJ (Table 2.1), we assumed there should be at least 10 nt matches on either side of the claimed BSJ. Approximately half (15/31, 48%) of the RNA-pull down probes did not meet this expectation, where 6 (40%) and 9 (60%) probes showed smaller matches to the 5' and 3' sides of the BSJ (Figure 2.15). Most of these probes (10/15, 66%) showed matches that differed by at least five nucleotides in length to the 5' and 3' sides of the BSJ (Figure 2.15). Three of these probes (PMID 35227262, 35821230, 36199071) showed matches that differed by more than 10 nucleotides (Figure 2.15).

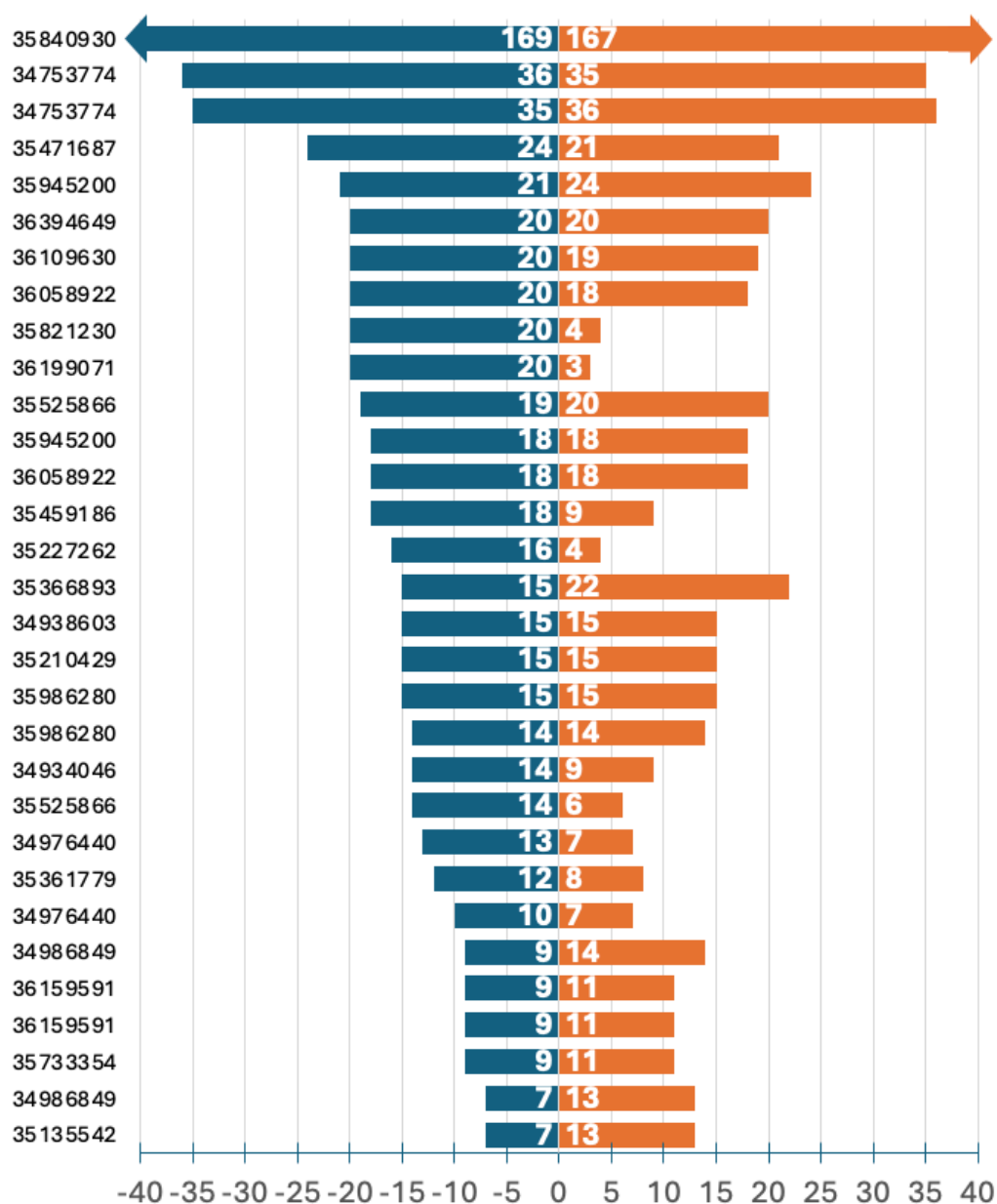


Figure 2.15. Summary of RNA pull-down probes according to the extent of sequence identity across the BSJ of the claimed circRNA target. Probes labelled by PMID (left) and mapped across the claimed BSJ (X-axis). Sequences 5' (negative numbers, X-axis) and 3' (positive numbers) are shown on either side of the BSJ (0 position). Matches to the 5'/3' side of the BSJ are shown in dark blue/orange, respectively, with match lengths shown in white. One probe of 336 nucleotides is partially shown (indicated by arrows).

2.3.3.5 2022 circRNA papers in high impact factor journals with wrongly identified cell lines

We verified the identities of 392 cell line descriptions in 90 circRNA papers, of which 15% (57/392) were predicted to be wrongly identified (Table 2.15). The 57 instances of problematic cell lines represented 27 unique cell lines, with the most frequent cell line being HepG2 (n=6), which was wrongly claimed to be a model of hepatocellular carcinoma (Supplementary Table 3.8). Almost all (51/57, 89%) wrongly identified cell lines were claimed as cancer cell lines, such as those from nasopharyngeal (17/51, 33%), liver (15/51, 29%), or gastric (11/51, 22%) cancers (Table 2.15). Most (44/57, 77%) wrongly identified cell lines were recognised as contaminated cell lines, typically by HeLa cells (40/44, 91%) as the sole contaminant (24/40, 60%) or in conjunction with another cell line of unknown origin (13/40, 33%) (Table 2.15). The most frequently identified HeLa-contaminated cell line was L02 (6/63, 10%), which was wrongly claimed as a liver cell line (Supplementary Table 3.8). Fewer cell lines (13/57, 23%) were misclassified, such as the HepG2 cell line (6/13, 46%) (Table 2.15, Supplementary Table 3.8).

The 57 descriptions of incorrect cell lines were distributed across 24% (22/90) circRNA papers that described cell lines, with a median number of 3 incorrect cell lines per paper (range: 1-7) (Table 2.15). Collectively, 51% (60/118) of screened papers described at least one problematic cell line and/or wrongly identified nucleotide sequence reagent, where most (14/22, 64%) papers with incorrect cell lines also described wrongly identified nucleotide sequences (Table 2.15, Supplementary Table

3.3). Most circRNA papers with incorrect cell lines were published open access (17/22, 77%) and studied a single cancer type (17/22, 77%) (Supplementary Table 3.3).

The 22 papers were published in 12 journals from four publishers, predominantly Springer Nature (7/12) (Supplementary Table 3.3). Just over a third of papers with wrongly identified cell lines (8/22, 36%) were published in two journals: *Molecular Cancer* (n=4, 2022 IF: 37.3) and *Cell Death and Discovery* (n=4, 2022 IF: 7) (Supplementary Table 3.3).

Table 2.15. Wrongly identified cell lines in 2022 circRNA papers in high-IF journals

Number of cell line descriptions analysed, n=	392
Proportion (percentage) of wrongly identified cell lines	57/392 (15%)
Proportion (percentage) 2022 circRNA papers that described human cell lines	90/118 (76%)
Proportion (percentage) of circRNA papers with cell lines that described wrongly identified cell lines	22/90 (24%)
Proportion (percentage) of papers with wrongly identified cell lines that also described incorrect nucleotide sequence(s)	14/22 (64%)
Wrongly identified cell lines per paper, median (range)	3 (1-7)
Contaminated human cell lines	44/57 (77%)
HeLa contamination	40/44 (91%)
HeLa as sole contaminant (e.g. SGC-7901, L02, SMMC-7721, BGC-823)	24/40 (60%)
Contamination by HeLa and cell line of unknown origin (e.g. CNE1, HONE1, 6-10B, S18)	13/40 (33%)
Contamination by HeLa and cell line of claimed identity forming a hybrid cell line (e.g. MGC803)	3/40 (8%)
Contamination by another cell line of claimed cancer type (e.g. K1, U373 MG, TE-13, Tu212)	3/44 (7%)
Partial contamination by mouse cells (e.g. SH-SY5Y)	1/44 (2.3%)
Misclassified cell lines (e.g. Caki-2, U87 MG, Hep3B)	13/57 (23%)
Hepatoblastoma cell lines claimed to be hepatocellular carcinoma (HepG2, HepG2.2.15)	7/14 (50%)
Claimed hepatocellular carcinoma cell line (SK-Hep-1) likely derived from endothelial cells	3/14 (21%)
Mismatch between RRID (research resource identifiers) and claimed identity (e.g. H2814/CVCL 6898)	3/14 (21%)
Proportion (percentage) of wrongly identified cell line descriptions according to claimed identity	
Cancer cells	51/57 (89%)
Nasopharyngeal (5-8F, 6-10B, CNE1, HONE1, CNE2, S26, S18, HNE1, HNE2)	17/51 (33%)
Liver (BEL-7404, SMMC-7721, SK-Hep-1, Hep3B, HepG2, HepG2.2.15)	15/51 (29%)
Gastric (e.g. MGC-803, BGC-823, SGC-7901)	11/51 (22%)
Lung squamous cell (Tu212, H2814, HCC520, LK2)	4/51 (8%)
Oesophageal (TE-13, EC9706)	2/51 (3.9%)
Parathyroid (K1)	1/51 (2.0%)
Neuroblastoma (SH-SY5Y)	1/51 (2.0%)
Normal cells (L-02)	6/57 (11%)

2.3.3.6 Non-verifiable cell line identifiers in 2022 circRNA papers in high impact factor journals

We identified 6 cell lines (1.5%, 6/392) in 6 circRNA papers whose identities were NV as they could not be found on Cellosaurus, ATCC, or Cellbank Australia (Supplementary Table 3.9). NV cell line identifiers were claimed to be cancer (4/6, 67%) or normal (2/6, 33%) cells (Table 2.16). Most NV cell line identifiers (5/6) were published in papers that also described wrongly identified nucleotide sequences (Table 2.16). We could not identify any similarly named cell lines for two NV cell line identifiers (HEB and CEC) (Table 2.16, Supplementary Table 3.9). We identified similarly named cell lines for four NV cell line identifiers (HFC, SW408, MKN87, GSE1), of which one (GSE1) was previously described as an NV cell line (Oste et al., 2024) (Table 2.16, Supplementary Table 3.9). As of December 2024, Google Scholar searches of all 6 NV cell line identifiers yielded 272 documents where these identifiers were mentioned, with each NV identifier being found in at least 10 indexed sources (Table 2.16).

Table 2.16. Non-verifiable cell line identifiers in 2022 circRNA papers published in high-IF journals

NV cell line identifier	Assumed/claimed identity	Similarly named cell line identity	Index paper - PMID/ DOI (error status)	Google Scholar and search string results, n= Dec, 2024
HFC	Colonic epithelial	FHC, colonic epithelial	35101080 (wrongly identified nucleotide sequences)	"HFC cell line", n=54
SW408	Colorectal cancer	SW480, colorectal cancer	35184406 (all verified reagents correctly identified)	"SW408", n=67
MKN87	Gastric cancer	MKN-45, gastric cancer	35354791 (wrongly identified nucleotide sequences and cell lines)	"MKN87", n=15
GSE1	Gastric epithelial	GES1, gastric epithelial (contaminated)	35780119 (wrongly identified cell lines)	"GSE1 cells" n=13
HEB	Glial	Unknown	35927233 (wrongly identified nucleotide sequences)	"HEB cell line", n=85
CEC	Endothelial	Unknown	https://doi.org/10.1016/j.snb.2022.132893 (wrongly identified cell lines)	"CEC cell line", n=38

2.3.3.7 Locations and affiliations of authors of 2022 circRNA papers in high impact factor journals

Of the 118 circRNA papers analysed, most (98/118, 83%) were authored by teams where the majority of authors were located in China (Supplementary Tables 3.3 and 3.4, Figure 2.16A). Significantly more circRNA papers where the majority of the authors were from China were also predominantly affiliated with hospitals (79/98, 81%), compared with papers from other countries (1/20, 5%) (Fisher's Exact Test, $p < 0.0001$, $n = 118$, Figure 2.16A). Echoing this, significantly more incorrect papers from China describing wrongly identified nucleotide sequences and/or cell lines were authored by hospital-affiliated teams (43/54, 80%), compared with papers from other countries (1/6, 17%) (Fisher's Exact Test, $p = 0.004$, $n = 60$, Figure 2.16B). We also observed this trend across circRNA papers with correctly identified reagents, where significantly more papers from China were authored by hospital-affiliated teams (36/44, 82%), compared with papers from other countries (0/14, 0%) (Fisher's Exact Test, $p < 0.0001$, $n = 58$, Figure 2.16C).

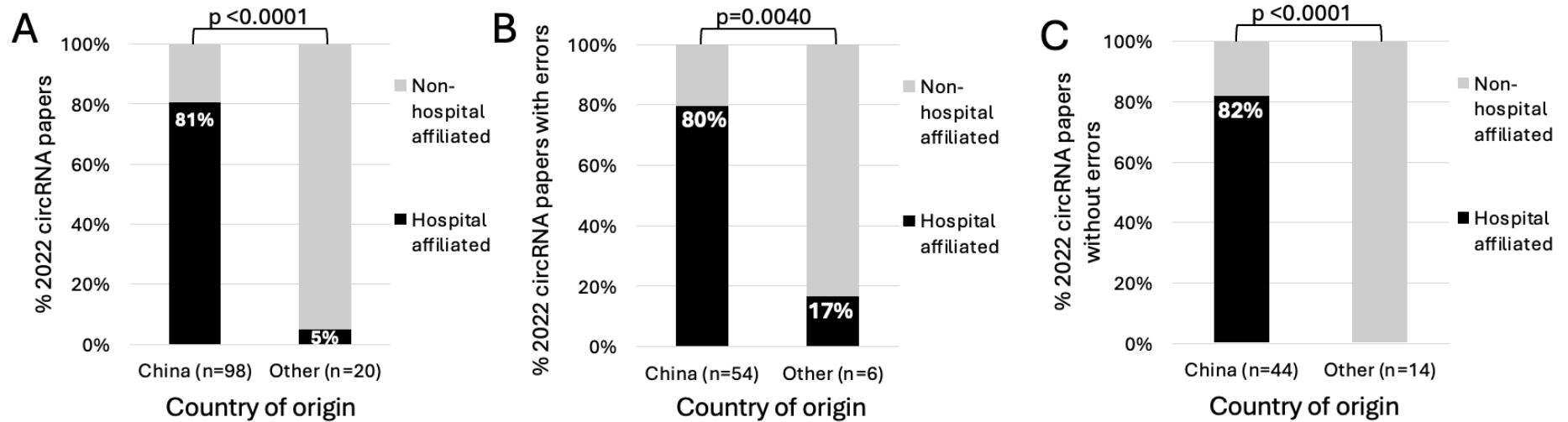


Figure 2.16. Features of 2022 circRNA papers in high-IF journals. Percentage of all (A) 2022 circRNA papers screened (Y-axis), (B) 2022 circRNA papers with errors (Y-axis) or (C) 2022 circRNA papers without errors (Y-axis) according to country of origin (X-axis, n=number of papers from China/other countries). Papers that were affiliated with hospitals are shown in black, with percentage values shown in white. Papers that were not affiliated with hospitals are shown in grey. Papers with errors are defined as describing wrongly identified nucleotide sequence reagents and/or cell lines. P-values = Fisher's Exact test.

2.3.3.8 Post-publication commentary and corrections of 2022 circRNA papers in high impact factor journals

Of the 60 papers with incorrect reagents (at least one wrongly identified nucleotide sequence reagent and/or cell line), almost all papers were recognised by PubPeer (58/60, 97%). Of the papers that were recognised by PubPeer, a minority (11/58, 19%) received comments on PubPeer, mostly (6/11, 55%) about the integrity of reported images (Table 2.17). One paper (PMID 35061934) also had comments describing wrongly identified cell lines that we identified in the present study (Table 2.17, Supplementary Table 3.3). Queries were also made on papers for methodological concerns (4/11, 36%) (Table 2.17, Supplementary Table 3.3). One paper (PMID 35024242) received PubPeer comments regarding ethical concerns and similarity of the paper to previous articles (Table 2.17, Supplementary Table 3.3).

Table 2.17. Summary of PubPeer comments on incorrect circRNA papers in high-IF journals

	circRNA Papers in high IF journals
Incorrect circRNA papers, n=	60
Proportion (percentage) incorrect circRNA papers recognised by PubPeer	58/60 (97%)
Proportion (percentage) incorrect circRNA papers with PubPeer comments	11/58 (19%)
Image integrity issues	6/11 (55%)
Wrongly identified cell line(s)	1/6 (17%)
Methodological concerns	4/11 (36%)
Wrongly identified nucleotide sequence(s)	1/4 (25%)
Citation of retracted references	1/11 (9%)
Ethical concerns and similarity to another article	1/11 (9%)

Two papers (PMID 35361779, 35710754) were retracted, and one paper (PMID 35210429) had a published correction between 19th September 2023 and 23rd September 2024 (Supplementary Table 3.3). Two papers (PMID 35361779, 35710754) were retracted for image concerns that had been previously raised by anonymous individuals on PubPeer (Supplementary Table 3.3). Neither retraction notice referenced PubPeer comments, although one notice (PMID 38910170) stated that the authors had retracted the article in response to queries and intended to publish a revised manuscript “in due course” (Supplementary Table 3.3). The other retraction notice (PMID 38326300) cited that the editors in chief retracted the article, noting ‘losing confidence in the integrity of the research presented in the article’ as concerns were raised about the figures and subsequent investigations where authors did not reply to concerns.

One paper (PMID 35210429) received a correction notice (PMID 35361760), deleting the published statement on equal contribution by authors (Supplementary Table 3.3). This paper also received a query on PubPeer regarding concerns over methodology, particularly the claimed identity of reagents targeting miRNAs that we also identified as being incorrectly identified in our current analysis (Table 2.17, Supplementary Tables 3.2, 3.3).

2.3.3.9 Citations and time to acceptance of 2022 circRNA papers in high impact factor journals

The 118 circRNA papers in high IF journals had been collectively cited 3,603 times, according to Google Scholar on 25th September 2024. The 60 incorrect circRNA papers were cited 1,559 times (1,559/3,603, 43%) and the 58 circRNA papers with correctly identified reagents were cited 1,886 times (2,044/3,603, 57%). Seven (7/60, 12%) incorrect circRNA papers were cited more than 50 times, with one paper (PMID 35768398) cited 106 times (Supplementary Tables 3.1A-B). We found no statistically significant difference in the number of citations of incorrect papers (median 21 citations/paper, range: 4-106, n=60) versus papers with correctly identified reagents (median 18 citations/paper, range: 1-331, n=58) (Mann-Whitney Test, U=1,723, p=0.9284).

We examined whether there were any differences between the time (in days) from submission to acceptance for 2022 circRNA papers with incorrect versus correct reagents. We found no statistically significant difference in the median times to acceptance for 2022 circRNA papers with incorrect reagents (median 126.5 days, range: 16-405, n=60) versus correct reagents (median 109 days, range: 10-298, n=58) (Mann-Whitney Test, U=1,409, p=0.0749, n=118) (Supplementary Tables 3.1A-B). The quickest time to acceptance for an incorrect circRNA paper (PMID 35101080) was 16 days by the *Journal of Translational Medicine*, whereas the longest time to acceptance was 405 days for a paper (PMID 36316334) in *Nature Communications* (Supplementary Tables 3.1A-B).

2.4 Discussion

2.4.1 Summary of results

We analysed papers in two high IF journals, *Molecular Cancer* (2014, 2016, 2018, and 2020) and *Oncogene* (2020) (Pathmendra et al., 2024), where 40 and 4 papers described nucleotide sequence reagents targeting human circRNA, respectively. We developed methods (Section 2.2.3, Figures 2.1, 2.2) to verify the identities of circRNA reagents, as their targeting requirements can differ from those of reagents targeting linear transcripts. Application of this method found that 40% (16/40) *Molecular Cancer* and 75% (3/4) *Oncogene* papers that studied circRNA(s) described at least one wrongly identified nucleotide sequence reagent (Tables 2.3, 2.18). Of the 16 incorrect papers in *Molecular Cancer*, 9 papers described at least one wrongly identified circRNA targeting reagent (Tables 2.4, 2.18, Sections 2.3.1.2, 2.3.1.3). We also identified 8 *Molecular Cancer* (8/40, 20%) papers with 17 NV sequence reagents (Tables 2.4, 2.18, Section 2.3.1.4), which is fewer than the 29 NV reagents identified in Pathmendra et al. (2024). This is due to an improvement in our previous methodology, resulting from the use of the specific circBASE ID provided to identify the transcript sequence via CircPRIMER (Zhong et al., 2018) or circATLAS (Wu et al., 2020) and conducting verifications manually. This allowed the verification of 12 circRNA targeting reagents that were previously classified (Pathmendra et al. 2024) as NV.

Table 2.18. Summary of the corpora screened and analysed, NA = Not Analysed

	<i>Molecular Cancer</i>	<i>Oncogene</i>	<i>Retracted circRNA</i>	<i>2022 circRNA papers</i>
Criteria for inclusion and subsequent analysis	Original papers (in 2018, and 2020) screened in Pathmendra et al. (2024) with circRNA targeting reagents	Original papers (in 2020) screened in Pathmendra et al. (2024) with circRNA targeting reagents	CircRNA papers in high IF (2022 IF \geq 7) journals retracted between 2016-31 July 2023	CircRNA papers in high IF (2022 IF \geq 7) journals with at least one nucleotide sequence reagent claimed to target a wild-type human transcript or genomic region, or use human cell lines
Number of screened papers, n=	40	4	13	118
Proportion (percentage) with nucleotide sequence reagents	40/40 (100%)	4/4 (100%)	12/13 (92%)	113/118 (96%)
Proportion (percentage) of analysed nucleotide sequence reagents that were wrongly identified	61/1,472 (4.1%)	7/162 (4.3%)	49/254 (21%)	201/3,370 (6.0%)
Proportion (percentage) of analysed NV nucleotide sequence reagents	17/1,472 (1.2%)	6/162 (3.7%)	12/254 (4.7%)	86/3,370 (2.6%)
Proportion (percentage) of screened papers with cell lines	NA	NA	13/13 (100%)	90/118 (76%)
Proportion (percentage) of analysed human cell lines that were problematic	NA	NA	6/52 (10%)	57/392 (15%)
Proportion (percentage) of screened papers with incorrect nucleotide sequences or cell lines	16/40 (40%)	3/4 (75%)	13/13 (100%)	60/118 (51%)
Proportion (percentage) of incorrect papers with majority of authors from China and affiliated with hospitals	14/16 (88%)	2/3 (67%)	12/13 (92%)	43/60 (72%)

We then analysed 13 circRNA papers in high IF journals that had been retracted as of July 31, 2023 (Table 2.18). All retracted papers described at least one wrongly identified nucleotide sequence reagent and/or cell line (Tables 2.7-2.9, 2.18, Sections 2.3.2.1, 2.3.2.2). However, none of the 11 retraction notices for papers with incorrect sequences mentioned any wrongly identified nucleotide sequences, and only one of 3 retracted papers with wrongly cited cell lines cited problematic cell lines as a reason for retraction (Table 2.10). Two retraction notices stated that authors recalled having communicated with third parties such as a “revision agency” (PMID 35592506) or “a third party provided the microscopy images in Fig. 4F” (PMID 36691006) that were not declared in the original papers. Notably, the retracted paper (PMID 32928266) described two wrongly identified nucleotide sequences that were not identified in the retraction notice (PMID 36691006) (Supplementary Tables 2.1 and 2.2). The other retraction notice (PMID 35592506) stated that “after communication with the ‘revision agency,’ the agency could not guarantee the uniqueness of the paper, including its data, charts, and photograph”. The corresponding paper (PMID 32059339) described one wrongly identified cell line that was not identified in the retraction notice (Supplementary Table 2.1).

Since 2016, the study of circRNAs has undergone rapid expansion (Figure 2.9A), with 1,276 original papers on circRNAs published in 2022 (Figure 2.9B). A small proportion (15%, 190/1,276) of these papers were published in high-IF journals. In the third and final section of this chapter, we analysed 118 circRNA papers published in 2022 in high IF journals that also described the use of at least one human cell line and/or nucleotide sequence reagent claimed to target a human gene/genomic region. We found that 46% (52/113) of circRNA papers described 201 (6.0%, 201/3,370) wrongly identified

nucleotide sequence reagents (Tables 2.11, 2.12, 2.18). This error rate is comparable to those previously described by Pathmendra et al. 2024 (31/74, 42% 2020 *Molecular Cancer* papers) and by Park et al. 2022 (31/163, 19% miR-145 papers published between 2009-2019). These 52 papers with wrongly identified nucleotide sequences were published across 28 journals (Table 2.13). Half (50%, 26/52) of the incorrect papers with wrong sequences described incorrect circRNA targeting reagents, mirroring similar proportions of circRNA papers found in *Molecular Cancer* in 2018 and 2020 (9/16, 56%, Table 2.3, Supplementary Table 1.2).

As also identified by Zhong et al. (2019), we identified incorrect circRNA reagents that were predicted not to discriminate between linear and circular transcripts, or divergent PCR primers that were predicted to function as convergent primers. We also identified 84 NV circRNA targeting reagents in 2022 circRNA papers due to unclear annotations of the claimed circRNA, where the specific transcript sequence and/or the BSJ could not be identified (Tables 2.14, 2.18). These results align with a previous analysis of cancer research papers that examined circRNAs, where some individual circRNAs could not be independently verified in papers published in 2015 (*circITCH*) and 2017 (*circBANP*) (Patop & Kadener, 2018).

Additionally, we decided to independently verify 392 human cell line identifiers described across 2022 circRNA papers (Tables 2.15, 2.18). We found that 15% (57/392) of human cell lines were wrongly identified in 24% (22/90) papers that described cell lines. Most papers also described at least one wrongly identified nucleotide sequence reagent (Table 2.15). In total, 60 circRNA papers in high IF

journals described at least one wrongly identified nucleotide sequence reagent and/or cell line (Table 2.18). Echoing the findings of previous studies from our team (Byrne & Labbé, 2017; Labbé et al., 2019; Park et al., 2022), most incorrect papers were published by teams with majority of authors from China, predominantly affiliated with hospitals. A small proportion (2/60) of incorrect papers were retracted throughout the analysis (19th September 2023 to 23rd September 2024), and one other paper received a correction notice (Section 2.3.3.8, Supplementary Table 3.3)—no notices referred to the errors identified in the present study.

2.4.2 The novelty of the findings

We are the first team to have developed methods to verify the identities of circRNA reagents (Pathmendra et al. 2024). The protocols developed in the present study build on and add to the methods of verifying nucleotide sequence reagent identities (Byrne & Labbé, 2017; Labbé et al., 2019; Park et al., 2022). Using such methods, we have discovered that most retracted circRNA papers in high IF journals have described many wrongly identified reagents that were not identified in the retraction notices or PubPeer comments. This suggests that reagent identities are overlooked and potentially not addressed through post-publication review. This included two papers with involvement from undeclared third parties, which, as noted by Han and Li (2018), are terms possibly synonymous with research paper mills. As such, it is possible that some papers describing incorrect reagents could be the product of research paper mills.

We are also the first to have conducted a large-scale analysis of reagent identities in circRNA papers published by high IF journals, where over half of the 2022 circRNA papers described at least one wrongly identified nucleotide sequence and/or human cell line. This further supports our hypothesis that incorrect circRNA papers can be found in high IF journals. By identifying an additional 30 high IF journals with incorrect circRNA papers, we demonstrate that poor publication quality of circRNA papers is not restricted to *Molecular Cancer* and *Oncogene*. We also found that these incorrect papers were cited at similar frequencies and accepted for publication over similar time frames as papers with no reagent errors.

In addition, we identified 2022 circRNA papers describing NV nucleotide sequences and cell lines. Notably, sequence reagent identifiers were largely NV due to unclear circRNA annotations, where a specific transcript could not be identified in external databases such as circBASE (Glažar et al., 2014) or circATLAS (Wu et al., 2020). Some NV circRNA sequence reagents used a specific ID provided by ArrayStar Inc., which resembles circBASE IDs but cannot be used to identify specific transcripts in external databases. We also identified 5 new NV cell line identifiers that were not found by Oste et al. (2024), which were also mentioned in numerous articles, as indexed by Google Scholar.

To our best knowledge, we are also the first to study circRNA targeting FISH, Northern blot and RNA-pull down probes (Section 2.3.3.4, Figures 2.14, 2.15) in circRNA research papers. It is expected that circRNA targeting reagents should show equivalent lengths of identity to both sides of the BSJ to effectively target the claimed

circRNA (Nielsen et al., 2022, Table 2.1), yet relatively few FISH (10/27, 37%) and RNA-pull down (7/31, 23%) probes satisfied the recommended targeting parameters outlined in Table 2.1 (Figures 2.14, 2.15, Section 2.3.3.4). We observed a broad range of probe lengths (Figures 2.14, 2.15), including some probes that showed unequal matches to one side of the BSJ compared to the other. Such imbalanced reagents seem unlikely to discriminate between linear and circular transcripts (Das et al., 2021; Gabryelska et al., 2024; Nielsen et al., 2022; Zirkel & Papantonis, 2018), potentially producing inaccurate results. In saying this, some probes could target the circRNA based on their specific melting temperature and thus could function potentially as claimed. Unlike the established targeting criteria for siRNAs and shRNAs (Figures 2.1, 2.2), we lack information about the targeting criteria for longer circRNA probes to make definitive predictions as to whether individual probes could discriminate between circular and linear transcripts.

2.4.3 The case for paper mill involvement

We recognise that wrongly identified nucleotide sequence reagents can occur in genuine research (Park et al, 2022), particularly when individual papers describe many individual reagents. However, the presence of problematic papers in high-IF journals could support the concern that paper mills may be successfully targeting some high-IF journals (Bricker-Anthony & Giangrande, 2022; Heck et al., 2021; Parker et al., 2024). In support, we found two retracted papers with wrongly identified reagents (not identified in retraction notices) in *Molecular Therapy Nucleic Acids* (PMID 32059339) and *Journal of Experimental and Clinical Cancer Research* (PMID 32928266). Both retraction notices detailed the undeclared involvement of a third party (Table 2.9,

Supplementary Table 2.1), which could be synonymous with a research paper mill (Han & Li, 2018). Hence, some other incorrect 2022 circRNA papers in high-IF journals could have originated from research paper mills.

Most of the screened 2022 circRNA papers in high IF journals were published by teams of authors from China (Figure 2.16A). Since 2016, the dramatic increase in circRNA publications has been primarily driven by authors in China (Figure 2.9B), confirming the bibliometric findings of Yehui et al. (2024) that China is a hotspot for circRNA research. We found significantly more incorrect 2022 circRNA papers from authors in China who were also likely to be affiliated with hospitals, compared with authors from other countries (Figure 2.16B). This echoes the broader literature around the phenomenon of ‘publish or perish’ (Aulakh, 2016) and how hospital-affiliated researchers in China might be subject to intense pressure to publish and could be resorting to third party organisations like paper mills (Hong et al., 2013; Parker et al., 2024; Yuan & Liu, 2023).

Given the significance of high IF publications to career development (Zhang et al., 2022), paper mills and clients could also value high IF journal publications, leading to a shift in focus by these illicit organisations. It has been proposed that IF partly dictates paper mill price strategies (Abalkina, 2023), suggesting that publications in high IF journals could be more lucrative than papers in lower IF journals. Another factor driving paper mill ‘interest’ in high IF journals could be the recognition that many lower IF journals have already been infiltrated by paper mills, resulting in either de-indexing from platforms like Web of Science (Kincaid, 2023) and policy actions by publishers

(COPE & STM, 2022; Flynn, 2023; Graf, 2023), and governments (Zhang et al., 2022). It has been reported that in China, there is now greater emphasis on publication in 'high-impact journals' as opposed to previously, when the emphasis was on the number of publications (Ro & Leeming, 2025). Given such contextual factors, and the rise of automated image and text generation tools powered by artificial intelligence (AI) (Eaton & Soulière, 2023; Grimaldi & Ehrler, 2023; Parker et al., 2024; Ro & Leeming, 2025), it is possible that at least some paper mills can produce seemingly high level manuscripts that can be accepted for publication by high IF journals.

2.4.4 The possible value of circRNA research to paper mills

It is already established that gene research is vulnerable to systematic research fraud (Byrne et al., 2019) (Section 1.2.5), due to the potentially repetitive nature of experiments and manuscripts that could be amenable to scaling. This was demonstrated in Byrne and Labbe (2017), where they discovered incorrect single-gene knockdown publications with high levels of textual and organisational similarity. We speculate that ncRNAs, particularly circRNAs could provide an additional layer of novelty to a preexisting template of gene research exploited by research paper mills (Figure 1.5) Pathmendra et al. 2024). Individual circRNAs can be linked to many proteins, and/or ncRNAs in the context of various diseases through their capacity to 'sponge' or bind targets (Dodbele et al., 2021; Fischer & Leung, 2017; Kristensen et al., 2022; Panda et al., 2017; Singh et al., 2024).

We identified numerous NV sequence reagents, mostly due to circRNA identities being poorly annotated, such that transcripts and claimed BSJ sequences could not be

verified independently. NV circRNAs reflect broader issues of incomplete and overlapping circRNA databases (Costa & Enguita, 2020; Dodbele et al., 2021; Pathmendra et al., 2024; Vromman et al., 2021) and non-standardised, multiple circRNA nomenclature systems (Chen et al., 2023; Costa & Enguita, 2020; Dodbele et al., 2021; Nielsen et al., 2022; Pathmendra et al., 2024; Vromman et al., 2021). Paper mills could exploit superficial circRNA descriptions to render the detection of poor-quality circRNA research more challenging. Whilst we cannot confirm whether the 60 incorrect 2022 circRNA papers that we identified originate from paper mills, this is a possibility given the presence of different types of errors and possible paper mill involvement in retracted circRNA papers with wrongly identified reagents.

2.4.5 Impacts on the field of circRNA research

Given the proposed regulatory roles of circRNAs, the study of circRNAs requires different reagents to study the circRNA itself and its associated targets (Drula et al., 2024; Fischer & Leung, 2017; Nielsen et al., 2022). This aligns with the fact that numerous incorrect circRNA papers with wrongly identified sequences and/or cell lines also claimed to study circRNAs in contexts such as within a regulatory “axis” or as a “sponge”.

Whilst honest errors in reagents identities could occur (Park et al. 2022), many errors found in the study seem unlikely to be made by expert biomedical researchers, such as reagents that were verified to target a different gene or even predicted to be non-targeting in humans (Figure 2.12). Such errors can be easily avoided using bioinformatic tools like Blastn, a skill widely taught in undergraduate studies in biology

and related fields (Niepielko & Shumskaya, 2021; Unger & Rollins, 2022). We were also surprised to discover circRNA reagents that did not map to the BSJ of the claimed circRNA target, despite the authors providing either the BSJ sequence or sufficient information to map the specific transcript via external databases (Table 2.12). We also found papers that described experiments with wrongly identified cell lines, that were mostly contaminated with HeLa cells (Table 2.15), a problem that has been widely recognised in the cancer research literature (Mirabelli et al., 2019). It is concerning to see descriptions of experiments with discredited cell lines, when such information is easily accessible through Cellosaurus (Bairoch, 2018).

Journals of high IF are often perceived as the “gold standard” of publication quality, in which many researchers strive to publish (Al-Awqati, 2007; Callaham et al. 2002). We noted that incorrect circRNA papers were cited at similar frequencies as papers with no reagent errors, suggesting that researchers are readily citing papers with problematic features. Given that circRNA research has grown exponentially in the past decade (Figure 2.9A), the presence of incorrect circRNA papers, published as recently as 2022, presents a serious threat to future research and its translation. The presence of NV sequences and cell lines (Tables 2.14, 2.16) indicates a lack of transparency in some circRNA papers. More than a quarter of the 2022 circRNA papers with NV nucleotide sequences also described wrongly identified sequences, and thus, some of the described research is likely to be irreproducible, beyond the presence of NV reagents.

We also discovered FISH and RNA-pull down probes that were poorly designed, where they showed uneven matches to the two sides of the claimed BSJ (Section 2.3.3.4, Figures 2.14, 2.15) or failed to meet the expected targeting criteria (Das et al., 2021; Gabryelska et al., 2024; Nielsen et al., 2022; Zirkel & Papantonis, 2018). Some of these probes appeared unlikely to discriminate between circular and linear transcript. Hence, even within the supposed “gold standard” of circRNA research in high IF journals, we found quality issues that could lead to the propagation of poor standards across the field. Such findings are concerning, as future researchers may use incorrect reagents or unreliable conclusions from papers in the “gold standard” literature, leading to a waste of resources and time (Byrne et al., 2019; Byrne et al., 2022).

The comparable times to acceptance between circRNA papers with wrongly identified reagents and no errors suggest that the current pre-publication review systems are overlooking these methodological errors and flaws in circRNA research. There is a clear need for more scrutiny of the methodological details in circRNA manuscripts. Most papers with wrongly identified nucleotide sequences or cell lines are also available via open access, where open-access articles available receive more readership than articles behind subscription pay-walls (Huang et al., 2024; Yi et al., 2024). This means problematic circRNA papers could be widely read. As such, the persistence of these problematic high IF circRNA papers, which are mostly available open access (Table 2.13), represents a breach of integrity within this field that needs to be addressed.

2.4.6 Limitations and future directions

We recognise that our ability to generalise conclusions about the integrity of all circRNA research is limited, given that high IF journals only represented a minority (16%) of journals from which we collated papers via our search strategy. In saying this, we also recognise that similar fundamental problems could be echoed in lower IF journals. Hence, future analysis of circRNA papers in lower IF journals could further clarify the extent of publication integrity concerns in the circRNA literature.

We recognise that some NV sequence reagents and poor-quality FISH and RNA-pull-down probes could reflect limitations of our fact-checking methods. In the cases of FISH and RNA-pull down probes, if the reagent mapped to the BSJ of the claimed circRNA, it was denoted as correctly identified. As this could generate false-negative observations, we then checked whether probes met recognised targeting criteria (Das et al., 2021; Gabryelska et al., 2024; Nielsen et al., 2022; Zirkel & Papantonis, 2018) outlined in Table 2.1. Few probes met the ideal criteria, signifying a significant mismatch between expected standards and the design of probes used in original circRNA papers. Some circRNA probes could be non-discriminative due to their unequal matches across the BSJ (Figures 2.14, 2.15). Given the lack of specific guidance around the minimal and maximal numbers of sequence matches for longer probes, it was difficult to judge whether such reagents discriminate between linear and circular transcripts. Hence, the observed error rates may be underestimated.

The field of circRNA research is growing, with a large majority of the original circRNA papers having been published by a few countries, notably China (Figure 2.9B) (Yehui

et al., 2024). We speculate that research involving circRNAs could be vulnerable to paper mill activity. The presence of wrongly identified and NV reagents, variations in the design of circRNA targeting probes, and inconsistent circRNA annotations could underpin superficial and poor-quality circRNA research. Current and future circRNA researchers could use these incorrect circRNA papers in high IF journals as models to construct their own manuscripts, thereby leading to the propagation of poor-quality research across the field.

As mentioned before, individual circRNAs could also be wrongly linked with other ncRNAs such as microRNAs (Singh et al., 2024) or signalling pathways implicated in diseases such as cancer (Li et al., 2021). As such, paper mills could create large numbers of manuscripts that appear complex and hence appealing to high IF journals by combining circRNAs, ncRNAs, protein-coding genes, and disease mechanisms, leading to the propagation of false conclusions about circRNA function. One of the prominently studied aspects of circRNA function involves claims that circRNA function as sponges for miRNAs (Singh et al., 2024). We found 11% of 2022 circRNA papers with wrongly identified sequences and/or cell lines claiming to study circRNA as a “sponge” of miRNAs.

However, as noted by Singh et al (2024), the low abundance of many circRNAs and the few miRNA binding sites on most circRNAs suggest that many circRNAs would not be able to effectively sponge miRNAs or other components of regulatory networks. As such, the popularisation of the concept of circRNA as sponges could be in part driven by poor-quality circRNA research papers, some of which may originate from paper

mills. This highlights the need to enhance the quality of reporting in specific circRNA papers that we and others have identified (Table 2.19). Furthermore, future investigations of features characteristic of known papers retracted for paper mill activity, including repeating patterns of authorship, could aid the detection of unreliable circRNA publications at scale. Journals should mandate standards to promote the full disclosure and accurate reporting of reagent identities (Table 2.19), where high IF journals are well placed to show leadership on best practices.

Table 2.19. Recommendations for improved reporting of circRNA sequences and circRNA targeting reagents in research publications (Pathmendra et al., 2024)

Problems	Proposed solutions
<ul style="list-style-type: none"> • Claimed circRNA target sequence could not be identified (Patop and Kadener, 2018) 	<ul style="list-style-type: none"> • circRNA sequences to be described in publications and deposited in external databases with clearly disclosed accession information (Dodbele et al., 2021; Vromman et al., 2021)
<ul style="list-style-type: none"> • Identities of claimed circRNA targets unclear or poorly described (Vromman et al., 2021) <ul style="list-style-type: none"> • Non-verifiable circRNA targeting reagents as claimed circRNA is presented in ID used in StarArray sequencing. 	<ul style="list-style-type: none"> • circRNA sequence descriptions to specify whether sequence is complete or partial • circRNA sequence descriptions to specify whether sequence is complete or partial • circRNAs to be identified by unique, recognized identifiers that disclose the host gene and the specific transcript on a publicly available database (Chen et al., 2023; Costa and Enguita 2020; Kristensen et al., 2018; Vromman et al. 2021) • circRNA identifiers to be accompanied by circRNA genomic coordinates, including reference genome build (Costa and Enguita 2020; Nielsen et al. 2022) • circRNA identifiers to be linked to database entries or define the nomenclature system used
<ul style="list-style-type: none"> • Case sensitive circRNA identifiers 	<ul style="list-style-type: none"> • circRNA database search algorithms to accept case-insensitive circRNA identifiers as queries
<ul style="list-style-type: none"> • circRNA reagents could not be verified as BSJ sequence not provided or unidentifiable on publicly available databases (Vromman et al. 2021) 	<ul style="list-style-type: none"> • circRNA descriptions to include transparent and verifiable information about BSJ sequence (Dodbele et al. 2021; Vromman et al. 2021) and provide a transcript specific circRNA ID that can be found on publicly available databases

Table 2.19 cont.

Problems	Proposed solutions
<ul style="list-style-type: none"> • Provided BSJ sequence information in publications is insufficient to conduct verification 	<ul style="list-style-type: none"> • Published BSJ sequences to disclose at least 5–16 nucleotides on each side of BSJ • circRNA databases to annotate BSJ at sequence level and define whether BSJ is predicted or experimentally verified
<ul style="list-style-type: none"> • BSJ sequences shown in images, i.e. flat files, not machine readable 	<ul style="list-style-type: none"> • BSJ sequences to be written in machine-readable format, preferably within the main text of publication
<ul style="list-style-type: none"> • Unclear targeting parameters for single circRNA targeting reagents 	<ul style="list-style-type: none"> • Single circRNA reagent descriptions to specify whether reagent targets the BSJ, or other circRNA feature (e.g. introns) not conserved in linear transcripts • Publications to cite published protocols or specific targeting parameters used to design probes, where they should justify any deviations to existing protocols
<ul style="list-style-type: none"> • circRNA targeting RT-PCR primers not specified as divergent or convergent 	<ul style="list-style-type: none"> • circRNA reagent descriptions to specify intended experimental use, including all reagents described in supplementary tables/files

2.4.7 Summary and conclusion

Research on circRNA is a highly technical and specialised aspect of gene research that has shown rapid progress within the last decade. As researchers continue to examine circRNAs in the context of various diseases, the literature must remain accurate and reliable. Despite the widely recognised concerns of using IF as a proxy for research quality (Ioannidis & Thombbs, 2019; Siler & Larivière, 2022), papers in high IF journals are perceived as the “gold standard” by many biomedical researchers (Al-Awqati, 2007; Callaham et al., 2002). Our results show that many circRNA papers in high-IF journals describe the use of wrongly identified nucleotide sequences and/or cell lines. As such, we encourage biomedical researchers to exercise caution when reading the circRNA literature, including papers published in high-impact-factor journals or with impressive citation numbers.

These findings support the need for education programs that actively discuss features of reliable publications and foster critical reading skills to combat the presence of problematic literature. Our results also suggest that high IF journals may also be vulnerable to paper mill activity, and we should avoid misplaced beliefs that paper mills are a problem limited to lower IF journals (Pérez-Neri et al., 2022). Considering this, we hope that, given their established brands and available resources, high-IF journals and their publishers will take the lead in responding to poor-quality publications. We believe that action from such journals will resonate and set benchmarks for the broader community, thus being critical in limiting the impacts and future publication of poor-quality circRNA papers.

Chapter 3: Do PubPeer posts influence post-publication corrections?

3.1 Introduction

The integrity of the scientific record and publishing relies on trust, with the expectation that science can self-correct (Merton, 1942). In the case of an erroneous paper, the most common course of action is to request that the journal publish a correction, an expression of concern, or a retraction (Townsend, 2013). A correction or erratum generally addresses minor errors or omissions in the published article that do not compromise the study's conclusions, often at the discretion of the author (Pierson, 2020). An expression of concern is typically a warning issued by editors when they identify more serious issues regarding the integrity or reliability of a publication, including situations where they may be unable to reach consensus with the study authors about an error (Noonan & Parrish, 2008). A retraction is the formal withdrawal of the published article, either at the author's or editor's discretion, often due to serious errors or misconduct (Wager et al., 2009).

Retrospective studies based on publications previously examined for fraud have shown high response rates from journals against papers confirmed for fraud and misconduct (Elia et al., 2014; Neale et al., 2007; Resnik & Dinse, 2013). However, a lower correction rate was observed by Bik et al. (2018), who found that only 10% of papers in molecular cancer and cellular biology journals with image integrity issues

were retracted. The slow response to correcting errors after publication is also evident in molecular oncology, where Byrne et al. (2021) observed that fixing a specific type of wrongly identified nucleotide sequence reagent error in cancer research papers can take years, and sometimes, the process is frustratingly slow.

Thus, processes for correcting published errors are challenging (Parker et al., 2022) and, in some cases, can take years (Ortega, 2021). As Byrne and Barnett (2024) point out, the presence of unreliable publications creates an unsafe workplace in the literature. Erroneous publications can pose a hazard to many researchers by misdirecting future scientific progress (Byrne et al., 2019, 2022), wasting valuable funds and resources (Freedman et al., 2015), and ultimately eroding trust in science (Davey, 2020).

Due to inefficient post-publication correction processes, researchers have turned to alternative systems for post-publication commentary. As noted by Brookes (2014), 23% of papers publicly discussed through an online blog received some editorial action compared to a journal response rate of 3.1% for papers that were discussed privately, suggesting that commentary using online platforms promotes publisher response. However, such commentary has become fragmented across various platforms, including online blog posts (Brookes, 2014), social media (such as Twitter/X; Brookes, 2025), and platforms designed to facilitate discussions of scientific articles, like PubMed Commons (da Silva, 2018) and PubPeer (Caron et al., 2024; Townsend, 2013). The most notable among these is PubPeer, which recently received the Einstein Foundation Institutional Award for its achievements (Einstein Foundation

Berlin, 2024). PubPeer is an online platform where individuals can post comments anonymously or publicly; authors of papers with PubPeer comments are notified via email and encouraged to respond (Caron et al., 2024; Stell, 2016).

A significant proportion of PubPeer posts have been described as queries about misconduct (Ortega, 2022). Consequently, there has been an expectation that activity on PubPeer prompts authors and/or publishers to take appropriate actions, such as corrections and/or retractions where necessary (Townsend et al., 2013). However, as noted by Ortega and Delgado-Quiros (2023), only 21.5% of publications from 2000 to January 2020 with PubPeer queries of error or potential misconduct received a post-publication editorial notice, implying limited impact of PubPeer comments on post-publication editorial actions.

This chapter builds on the work of two studies: Byrne et al. (2021) and Ortega and Delgado-Quiros (2023). Byrne et al. (2021) conducted a retrospective analysis to examine how different journals responded to email descriptions of a specific type of wrongly identified nucleotide sequence. Conversely, Ortega and Delgado-Quiros (2023) provided a retrospective, descriptive analysis of PubPeer comments related to subsequent editorial actions. However, they did not consider additional communication between authors, editors, and PubPeer posters that may have prompted such responses. Therefore, given their retrospective nature, these studies cannot be used to establish a causal link between commentary and editorial action.

To our knowledge, no prospective study has examined whether posting comments on PubPeer, alongside email notifications sent to editorial offices, prompts editorial action. Therefore, to fill this gap, we designed a prospective study to evaluate the effects of posting PubPeer notices in addition to email notifications, sent at specific times. In this chapter, we describe a trial in which we initially sent an email notification to the journals *Molecular Cancer* and *Oncogene* regarding errors (wrongly identified nucleotide sequence reagents) in publications described in Pathmendra et al. (2024). Papers with errors were then assigned to two groups, where both groups received PubPeer comments, with comments for one group being posted six months after comments for the earlier group. We aimed to determine whether journals (*Molecular Cancer* and *Oncogene*) respond more frequently or more quickly to PubPeer notices compared with only email notifications. Overall, this will help us to assess any possible causal effects of PubPeer commentary on post-publication editorial actions.

3.2 Methods

3.2.1 Collation and selection of articles into study arms

We gathered all original articles from *Molecular Cancer* and *Oncogene* that described at least one wrongly identified nucleotide sequence reagent that we had previously identified (Pathmendra et al., 2024). Articles were eligible if they: i) described at least one wrongly identified nucleotide sequence reagent that had not been corrected or retracted before January 2023, and ii) had not been previously posted on PubPeer by our team. Papers with only NV nucleotide sequences and no incorrect reagents were excluded from the study. Articles were organised by journal and ranked in order of ascending PubMed ID (PMID) in MS Excel to ensure similar publication dates in the two study arms. Based on the outcome of a coin flip, we assigned every odd-numbered row to arm one and every even-numbered row to arm two of the study. Arm 1 papers received PubPeer comments posted at baseline, and Arm 2 papers received PubPeer comments posted six months after baseline.

3.2.2 Study design

We first emailed the editors-in-chief of *Oncogene* and *Molecular Cancer* on 16 March 2023, sharing a supplementary file detailing the incorrectly identified nucleotide sequences for 117 papers and referencing the associated preprint (Pathmendra et al., 2023) (Figure 3.1). We included details about NV sequence reagents in the PubPeer post for 5 papers, in addition to the wrongly identified nucleotide sequence reagents. We then uploaded PubPeer comments for Arm 1 papers on 05 April 2023. PubPeer comments for Arm 2 papers were uploaded on 04 October 2023 (Figure 3.1). For the

paper (PMID 30470262), the authors had provided new, wrongly identified nucleotide sequence reagents in the correction notice (PMID 33126881), and therefore, we posted PubPeer comments that were linked to both the article and the correction notice. We set up PubPeer auto-alerts for each queried article so that PP received an email if authors responded or if other PubPeer posts (not by our team) were made throughout the study period. Each response was coded by PP according to the author response claims outlined in Table 3.1. In cases of doubt, discussions with JAB were held to classify author responses according to these five categories.

Throughout the study period (05 April 2023 to 31 July 2024), we also addressed authors' comments on PubPeer, as shown in Table 3.1. Where authors agreed with our claims of incorrectly identified reagent(s) (Table 3.1), we did not respond further to avoid influencing journal responses due to increased communication between the authors and our team. PubPeer responses were written by PP and reviewed by JAB before replies were posted within 2 weeks of the author's response on PubPeer. The study was planned to be completed one year after commencement on 03 April 2024. However, the study was extended until July 31, 2024, approximately six months after the publication date Pathmendra et al. (2024), as the publication of our earlier preprint could have potentially affected journal responses.

Table 3.1. Summary of team responses to the author's PubPeer responses

Author Response	Team response
Acknowledged claimed error(s) and/or provided new sequence(s)	No response
Stated intent to follow up and investigate further	No response
Acknowledged some claimed error(s) but denied other claimed error(s)	No response
Denied all claimed errors	Explained claimed error(s), cited methods used to verify reagent identities
PubPeer posts described false positive results where reagent(s) were correctly identified but incorrectly claimed as error by our team	Acknowledged false positive claims, highlighted possible source of errors by team.

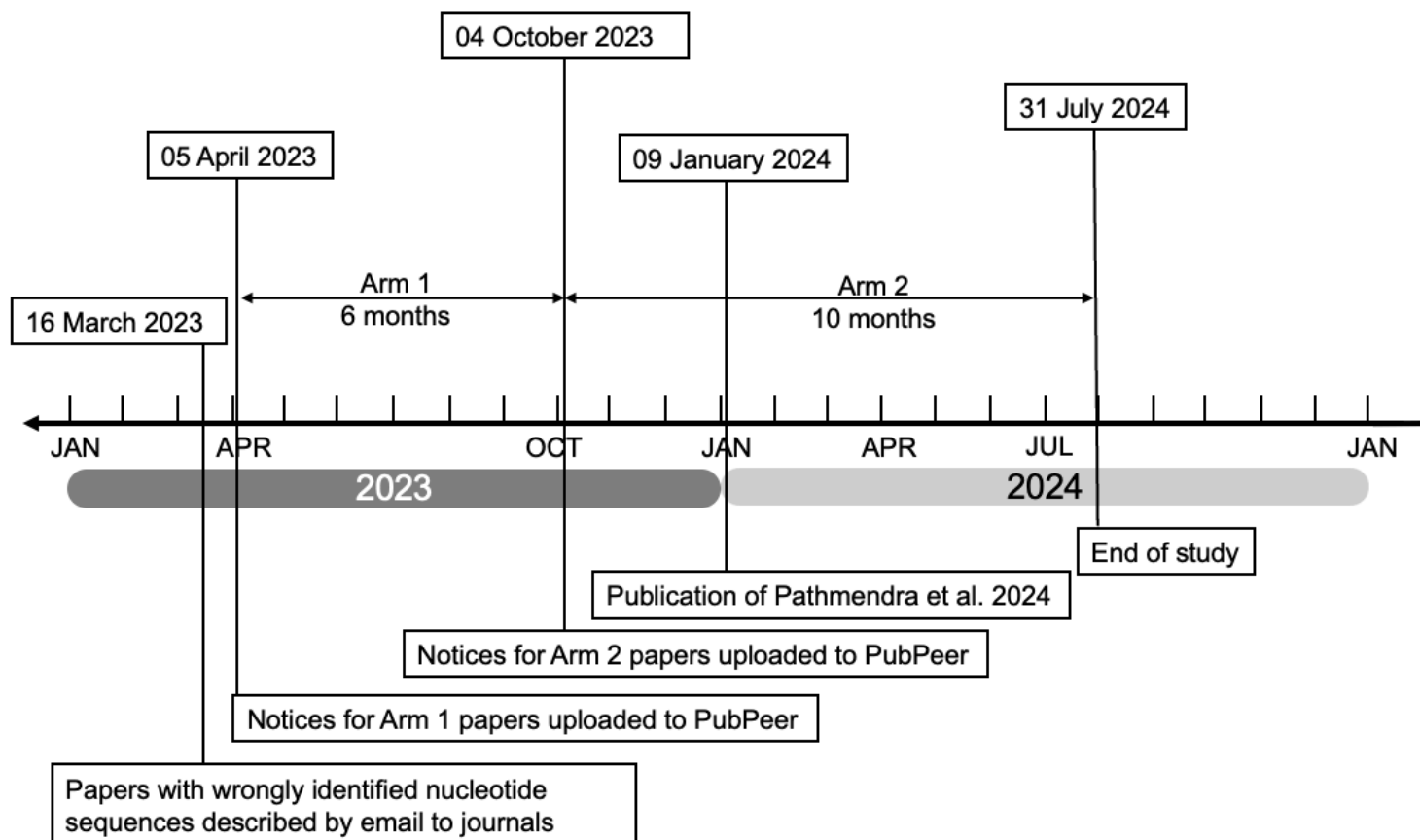


Figure 3.1. Diagrammatic representation of the timeline of the study. Years are shown as grey boxes below the timeline, with each dash representing one month. Text describes key events (below) and associated dates (above).

3.2.3 PubPeer comments

PP drafted PubPeer posts using MS Word, and JAB reviewed each comment. Briefly, each comment included the reagent sequence and the claimed identity, as stated in the queried paper, along with our verification results (Figure 3.2) (Pathmendra et al., 2023). We included the genomic location of the claimed target gene (according to GeneCards, Stelzer et al. 2016) and the relevant genomic assembly, where required (Figure 3.2). We also included NV nucleotide sequence(s). At the end of each comment, we noted possible origin(s) of these errors and relevant publications (Figure 3.2) (Byrne et al., 2021; Park et al., 2022; Pathmendra et al., 2023). We declared each comment had been written by the PRIMeR group (Figure 3.2).

#1 PranuJan Pathmendra comment accepted October 2023

The following nucleotide sequence reagent mentioned in this paper appears to be wrongly identified:

1. Real Time PCR reverse primer 5'- CCTTCTTGGTCCGCCGTTCTTA-3'

- claimed to target human FGF4 (chr11:69,771,022-69,775,341(GRCh38/hg38))
- predicted to be non-targeting in human
- predicted to target FGF4 in other species including *Rattus rattus*, *Mastomys coucha*

The identity of this nucleotide sequence was verified as described (Byrne et al. 2021, Park et al. 2022, Pathmendra et al. 2023). We recognise that nucleotide sequence analyses rely on algorithms and databases that may be subject to updates.

This wrongly identified reagent might reflect an error that occurred during manuscript preparation only, or more critical issues that could question the validity of the results.

This comment was written by the PRIMeR group

Figure 3.2. Example of PubPeer comment posted for PMID 25491321 (Arm 2)

3.2.4 Data collection and analysis

3.2.4.1 Excluded publications

One *Molecular Cancer* paper allocated to Arm 1 and one *Molecular Cancer* paper in Arm 2 were retracted before April 2023 on 20 March 2023 and 01 February 2023, respectively, and were therefore excluded from analysis. Papers allocated to Arm 2 that were retracted between 05 April 2023 and 04 October 2023 (Arm 1, Figure 3.1) were included, as editors had acted during the study period.

3.2.4.2 PubPeer responses

All papers were reviewed to determine whether they had a corresponding email address, as also indicated by a blue tick on the corresponding PubPeer profile. We recorded the content of all PubPeer responses to our posts, as well as the names of contributors and the response dates (month and year). We also recorded the contents of PubPeer posts by other contributors before and during the study (until July 31, 2024).

Responses from authors were recorded in MS Word. Author responses were categorised as: i) complete corrections, where authors provided new sequence(s) for all queried wrongly identified reagent(s); ii) partial corrections, where authors provided correct sequence(s) for at least one sequence but denied error claims for at least one sequence; iii) general responses, where authors made no corrections or did not address claimed error(s); and iv) no response. For all papers with an author response on PubPeer, we recorded whether the authors disclosed any intent to publish a

correction, and whether they claimed that wrongly identified nucleotide sequence reagent(s) did not affect key results and conclusions of the study. We also noted any author explanation regarding the source of the error(s).

Where authors provided corrected nucleotide sequences, we manually verified each corrected sequence as described in Section 2.2.3 and recorded whether the substituted reagents were correctly identified in the correction. We assessed whether author corrections aligned with the methods in the original article, using any supporting material supplied by the authors, such as screenshots of sequence alignments. Where authors rejected claims that reagent(s) were wrongly identified, we recorded the primary reason and whether PP and JAB agreed that our claimed errors were false-positive observations. If authors gave a general response, we noted whether the response acknowledged the described error(s) and/or whether the authors claimed to have conducted any follow-up investigation(s). All data were recorded in MS Word and/or MS Excel.

3.2.4.3 Journal responses

Post-publication responses were defined as a journal publishing a correction, retraction or expression of concern addressing any errors in a study paper. For each post-publication notice published prior to and during the study period, we recorded the notification content and the date of publication (month and year, as per the journal's website). We examined the associated PubPeer comment(s) to determine whether the error(s) addressed in the post-publication notice had been described on PubPeer (either by us and/or others). For corrections in response to our queries about

nucleotide sequence reagent identities, PP assessed the plausibility and accuracy of the corrections by verifying the identities of any corrected sequences according to the methods outlined in Sections 2.2.3 and 2.2.4 (Park et al. 2022). We also reviewed notices to determine whether author(s) agreed with the editorial decisions. All data was recorded on MS Excel.

3.2.5 Statistical and Additional Analyses

We first calculated the numbers and proportions of study papers by year of publication and journal. The Fisher's Exact Test and Chi-Squared test were used to compare distributions of papers across Arms 1 and 2 according to the journal and publication year, respectively. We also calculated the median number of sequences described per study paper, and proportions and numbers of reagents according to claimed identity, reagent and error type. We described the proportions of study papers that included NV reagents and the number of NV reagents queried on PubPeer by our team.

We calculated the numbers and proportions of papers with PubPeer posts prior to and during the study according to content, author response status, time taken for authors to respond (in months), whether authors intended to seek a published correction, publication year and/or journal. A Chi-Squared test was used to compare the proportions of *Molecular Cancer* study papers with/without author responses to PubPeer posts made by our team according to publication year. A Fisher's Exact Test was used to compare proportions of study papers with/without author responses according to the journal of publication, whether the paper had prior PubPeer posts, and the author response status to prior posts.

We calculated the numbers and proportions of papers with published corrections prior to the study, and any editorial notice during the study, according to content and whether the notice described errors flagged on PubPeer (by others or our team). We calculated the numbers of papers with author responses on PubPeer declaring an intent to seek published correction and whether a correction was issued during the study period. The time from publication to when the post-publication notice was published was calculated in days, months and/or years per paper. For papers with published corrections prior to the study, we calculated a median time (in days or months and years) from publication to correction. Where possible, we reported on the times to correction, i.e. the difference in time between the publication of the post-publication notice and the time of the earliest PubPeer flagged error addressed in the notice in months and/or years. Calculations were performed on MS Excel. All statistical tests were performed on GraphPad PRISM 10.5.0.

3.3 Results

3.3.1 Cohort description

Of the 112 papers with wrongly identified nucleotide sequence reagents identified in Pathmendra et al. (2023), 107 papers were allocated to the study. Of these, 53 papers in Arm 1 and 52 papers in Arm 2 were included for analysis, as they had not been retracted and the identified incorrect sequences had not been corrected prior to the study commencing on 05 April 2023. Most papers allocated to Arms 1 (42/53, 79%) and 2 (42/52, 81%) were published in *Molecular Cancer*, with the remaining papers published in *Oncogene* (Arm 1: 11/53, 21%, Arm 2: 10/52, 19%) (Table 3.2). Papers were similarly distributed between Arms 1 and 2 according to journal (Fisher's Exact Test, $p > 0.9999$) and publication year ($\chi^2 = 0.2109$, $df = 3$, $p = 0.9758$) (Table 3.2). Approximately two-thirds (35/53, 66%) and most (42/52, 81%) papers in arms 1 and 2, respectively, were authored by teams where the majority of authors were located in China.

The 53 papers in Arm 1 and 52 papers in Arm 2 described 124 and 149 wrongly identified nucleotide sequence reagents, respectively, with a median of 2 incorrect sequences per paper (Arm 1 range: 1-11, Arm 2 range: 1-14) (Table 3.2). Most incorrect reagents were PCR primers (Arm 1: 104/124, 84%, Arm 2: 123/149, 83%) (Table 3.2). Most incorrect sequences were either claimed targeting reagents that were predicted to target a different transcript or genomic sequence (Arm 1: 74/124, 60%, Arm 2: 72/149, 48%) or predicted to be non-targeting in human (Arm 1: 50/124, 40%, Arm 2: 75/149, 50%) (Table 3.2). Two papers in Arm 2 described one claimed

non-targeting reagent that was predicted to target a human gene (Table 3.2, Supplementary Table 4.1). Most incorrect claimed targeting sequences that were queried on PubPeer were claimed to target protein-coding genes, including associated genomic elements such as promoters and introns (Arm 1: 95/124, 77%, Arm 2: 107/147, 73%) (Table 3.2).

We also queried 15 and 4 NV reagents that were described in 3 Arm 1 and two Arm 2 papers, respectively (Table 3.2). All NV sequences were claimed to target human circRNAs.

Table 3.2. Characteristics of study papers.

	Arm 1	Arm 2
Number of allocated papers	54	53
Number of analysed papers	53	52
Proportion (percentage) of study papers according to journal and year of publication		
<i>Molecular Cancer</i>	42/53 (79%)	42/52 (81%)
2014	15/42 (36%)	15/42 (36%)
2016	3/42 (7%)	3/42 (7%)
2018	11/42 (26%)	9/42 (21%)
2020	13/42 (31%)	15/42 (36%)
<i>Oncogene, 2020</i>	11/53 (21%)	10/52 (19%)
Proportion (percentage) of study papers according to the country where majority of the authors are from		
China	35/53 (66%)	42/52 (81%)
USA	6/53 (11%)	1/52 (1.9%)
Other countries	12/53 (23%)	9/52 (17%)
Number of wrongly identified nucleotide sequence reagents queried	124	149
Claimed targeting reagents predicted to target a different human transcript, or genomic sequence	74/124 (60%)	72/149 (48%)
Claimed targeting reagents predicted to be non-targeting in human	50/124 (40%)	75/149 (50%)
Claimed non-targeting reagents predicted to target a human gene	0/124 (0%)	2/149 (1.3%)
Proportion (percentage) of wrongly identified reagents according to reagent type		
PCR primers	104/124 (84%)	123/149 (83%)
Single sequence reagents	20/124 (16%)	26/149 (17%)
Number of wrongly identified reagents that were claimed to target a gene/genomic region	124	147
Protein-coding gene and associated genomic elements (promoters, introns)	95/124 (77%)	107/147 (74%)
miRNAs	13/124 (10%)	21/147 (14%)
circRNA	6/124 (4.8%)	12/147 (8%)
Other ncRNAs	6/124 (4.8%)	7/147 (4.8%)
Genomic regions	3/124 (2.4%)	0/147 (0%)
Wrongly identified sequence reagents queried per paper, median (range)	2 (1-11)	2 (1-14)
Proportion (percentage) of study papers with NV nucleotide sequences	3/53 (5.7%)	2/52 (3.8%)
Number of NV nucleotide sequence reagents	15	4

3.3.2 PubPeer comments prior to study commencement

3.3.2.1 Description of PubPeer posts made prior to the study

Prior to the study commencing on 05 April 2023, 11% (6/53) and 40% (21/52) of papers in Arms 1 and 2, respectively, already had 16 and 96 PubPeer posts (Table 3.3). Two-thirds of Arm 1 papers (4/6, 67%) and 86% of these Arm 2 papers (18/21) were published in *Molecular Cancer*, with all remaining papers published in *Oncogene*. The median number of PubPeer posts per paper before the study commencement was 3 in both arms (Arm 1 range: 1-4, Arm 2 range: 1-14) (Table 3.3).

Most PubPeer posts made prior to the study commencement described possible errors in the papers (Arm 1: 13/16, 81%; Arm 2: 73/96, 76%). Two-thirds (4/6) of papers in Arm 1 and nearly all (20/21) papers in Arm 2 with prior PubPeer posts raised concerns about image integrity (Table 3.3). In contrast, few papers had prior PubPeer posts (Arm 1: 2/6, 33%, Arm 2: 3/21, 14%) that mentioned wrongly identified nucleotide sequence reagents (Table 3.3). One paper in Arm 2 (PMID 24650096) with a prior PubPeer post concerning wrongly identified nucleotide sequence reagents was subsequently found to be a false positive observation, where the anonymous poster who had identified the query had mistakenly interpreted the sequence orientation in their analysis (Supplementary Tables 4.1, 4.2, Figure 3.3)

Most papers with prior PubPeer posts to the study commencement had no responses from authors (Arm 1: 5/6, 83%, Arm 2: 11/21, 52%). Of the papers with prior PubPeer posts where authors responded (Arm 1: 1/6, 17%, Arm 2: 10/21, 48%), authors

generally accepted the error claim and indicated an intention to contact the editorial office, and publish a correction (Arm 1: 1/1, Arm 2: 5/10) or asked whether they should consult the journal to publish a correction (Arm 2: 1/10) (Figure 3.3, Supplementary Table 4.1). For three papers in Arm 2 (3/10), the authors posted general replies stating their intent to conduct follow-up investigations and clarify the queried error, where only one paper's authors (PMID 32019579) provided a detailed explanation, acknowledging the error within the month of the author's response (Figure 3.3). Two papers in Arm 2 had PubPeer posts where the authors denied the claim of error(s).

3.3.2.2 Response timeframes on PubPeer

Five papers (5/6, 83%) in Arm 1 and approximately half of the papers (10/21, 48%) with PubPeer posts prior to the study were published in 2020 (Supplementary Table 4.1). Conversely, a lower proportion of papers in Arm 2 (7/21, 33%) with PubPeer posts prior to the study were published in 2014 (Supplementary Table 4.1). Across most papers with author responses across both arms (Arm 1: 1/6, 17%, Arm 2: 10/21, 48%), the authors replied to PubPeer posts within one month of the post (Arm 1: 100%, 1/1; Arm 2: 80%, 8/10) or by the following month (arm 2: 20%, 2/10) (Figure 3.3). Most papers where authors responded to prior PubPeer queries were published in 2020 (Arm 1: 1/1, Arm 2: 6/10) (Figure 3.3, Supplementary Table 4.1).

Table 3.3. Summary of study papers with PubPeer queries before study commencement (April 05, 2023).

	Arm 1	Arm 2
Number of papers	53	52
Proportion (percentage) papers with at least one PubPeer query before study commencement	6/53 (11%)	21/52 (40%)
Total number of PubPeer posts made prior to the study	16	96
Number of PubPeer posts per paper with PubPeer queries prior to study commencement, median (range)	3 (1-4)	3 (1-14)
Proportion (percentage) papers with prior PubPeer queries according to post content		
Posts about errors	6/6 (100%)	21/21 (100%)
Image Integrity	4/6 (67%)	20/21 (95%)
Wrongly identified nucleotide sequence reagents	2/6 (33%)	3/21 (14%)
Methods	2/6 (33%)	2/21 (10%)
Author responses to PubPeer posts	1/6 (17%)	10/21 (48%)
Accepted claimed error(s)	1/1 (100%)	6/10 (60%)
Denied claimed error(s)	0/1 (0%)	2/10 (20%)
Expressed intention to follow-up	0/1 (0%)	3/10 (30%)

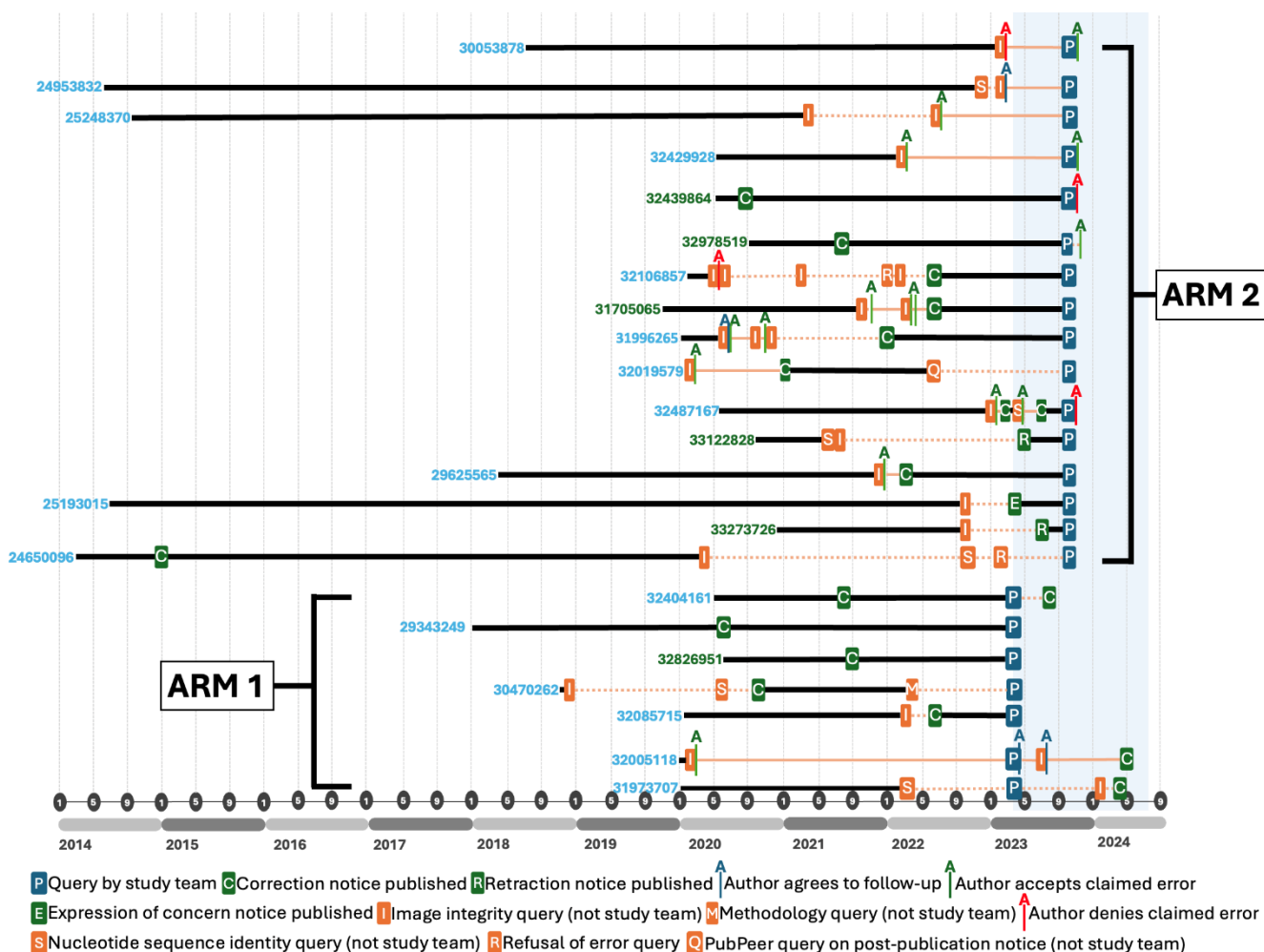


Figure 3.3. Diagrammatic representation of papers with PubPeer posts that were responded to by authors prior to the study commencement (05 April 2024) or had a post-publication notice (before 31 July 2024). X-axis, years; numbers indicate months. Each horizontal line depicts a paper shown by PMID (green = *Oncogene*, blue = *Molecular Cancer*). Black lines represent time from publication to first PubPeer query, or from post-publication notice to subsequent PubPeer post. Times between PubPeer posts and post-publication notices are shown by orange lines (dashed = no response from authors on PubPeer, solid = authors responded). The blue-shaded area to the right shows the duration of the current study. Symbols are defined below the X-axis. Multiple posts of the same error type within one month were not shown individually, allowing data presentation.

3.3.3 Analysis of post-publication notices prior to the study commencement

3.3.3.1 Description of the correction notices

Five papers (5/53, 9%) in Arm 1 and 9 papers (9/52, 17%) in Arm 2 had a correction notice published before the study's commencement (Figure 3.3). Most of the papers with correction notices were published in either 2018 (Arm 1: 2/5, Arm 2: 1/9) or 2020 (Arm 1: 3/5, Arm 2: 7/9), where one Arm 2 paper with a correction was published in 2014. Most correction notices (Arm 1: 4/5, 80%, Arm 2: 7/9, 78%) explicitly stated that the correction of errors did not affect the study findings or conclusions (Supplementary Table 4.1). Most correction notices addressed image integrity concerns (Arm 1: 4/5; Arm 2: 8/9), with two other corrections addressing typographical errors (Supplementary Table 4.1). One correction notice for a paper in Arm 1 with image integrity concerns also provided new nucleotide sequences, replacing incorrectly identified reagents that were queried by anonymous commentators on PubPeer (Supplementary Table 4.1). However, we discovered that one of the corrected nucleotide sequences was incorrectly identified within the correction and was thus reported in this study.

Some correction notices (Arm 1: 2/5; Arm 2: 6/9) addressed errors such as image integrity issues and/or wrongly identified nucleotide sequence reagents previously flagged on PubPeer by others. No notices with PubPeer-flagged errors referenced the associated PubPeer threads. Instead, some authors claimed that they had identified the error themselves (Arm 1: 1/2; Arm 2: 4/6, Supplementary Table 4.1). For two

papers in Arm 2, where authors accepted the error claim and intended to seek published correction, no editorial notices were published by 31 July 2024 (Figure 3.3).

3.3.3.2 Timeframes of post-publication correction

The 14 papers with corrections prior to the study commencement (Arm 1: 5/14, 36%, Arm 2: 9/14, 64%) had a median correction time (from first PubPeer error query to correction) of 706 days (range: 112-1455 days), or approximately 23 months (range: 3-47 months). For the 8 papers with corrections addressing PubPeer-flagged errors (Arm 1: 2/8, Arm 2: 6/8), the median correction time was 7 months (range: 2-22 months) (Figure 3.3, Supplementary Table 4.1).

3.3.4 PubPeer posts during the study

Most PubPeer posts by the study team did not receive author responses (Arm 1: 38/53, 72%; Arm 2: 41/52, 79%) during the study period (05 April 2023 to 31 July 2024) (Table 3.4). Proportions of *Molecular Cancer* study papers that received no author responses decreased across publication years, where significantly fewer 2014 papers received author responses to our PubPeer queries than any other year (Figure 3.4, $\chi^2=13.13$, $df=3$, $p=0.0044$). Papers with no author responses typically only received posts from our team during the study (Arm 1: 36/38, 95%; Arm 2: 34/41, 83%, Table 3.4). Most 'no response' papers had no earlier PubPeer posts questioning errors before our comments (Arm 1: 33/38, 87%; Arm 2: 23/41, 56%, Table 3.4, Supplementary Table 4.1). Over one third of 'no response' papers in Arm 2 (18/41, 44%) had prior PubPeer queries about errors, yet most of these queries (11/18, 61%) went unanswered by the authors (Table 3.4).

Three papers in Arm 1 received correction notices, addressing queries related to the errors that we described on PubPeer. For two of these papers, the authors did not respond on PubPeer (Table 3.4, Figures 3.2, Supplementary Table 4.1). Two Arm 2 papers were retracted, one paper received an expression of concern, and another paper received a correction that did not address the errors that we described in our PubPeer post (Table 3.4, Figures 3.2, Supplementary Table 4.1). We will review the details of these post-publication notices in Section 3.3.5.

Table 3.4. Summary of papers with no author responses to PubPeer queries during the study (05 April 2023 to 31 July 2024).

	Arm 1	Arm 2
Number of papers	53	52
Proportion (percentage) of papers that did not receive any author responses	38/53 (72%)	41/52 (79%)
No post-publication notices during the study	36/38 (94%)	38/41 (93%)
PubPeer posts from our team only	36/38 (94%)	34/41 (83%)
No post-publication notices prior to study commencement	33/38 (87%)	35/41 (85%)
No PubPeer posts prior to study commencement	33/38 (87%)	23/41 (56%)
PubPeer posts prior to study commencement	5/38 (13%)	18/41 (44%)
No responses from authors	5/5 (100%)	11/18 (61%)
Post-publication notices during the study	2/38 (5%)	3/41 (7%)
Correction addressing errors flagged on PubPeer	2/2 (100%)	0/3 (0%)
Retraction addressing errors flagged on PubPeer	0/2 (0%)	2/3 (67%)
Expression of concern addressing errors flagged on PubPeer	0/2 (0%)	1/3 (33%)

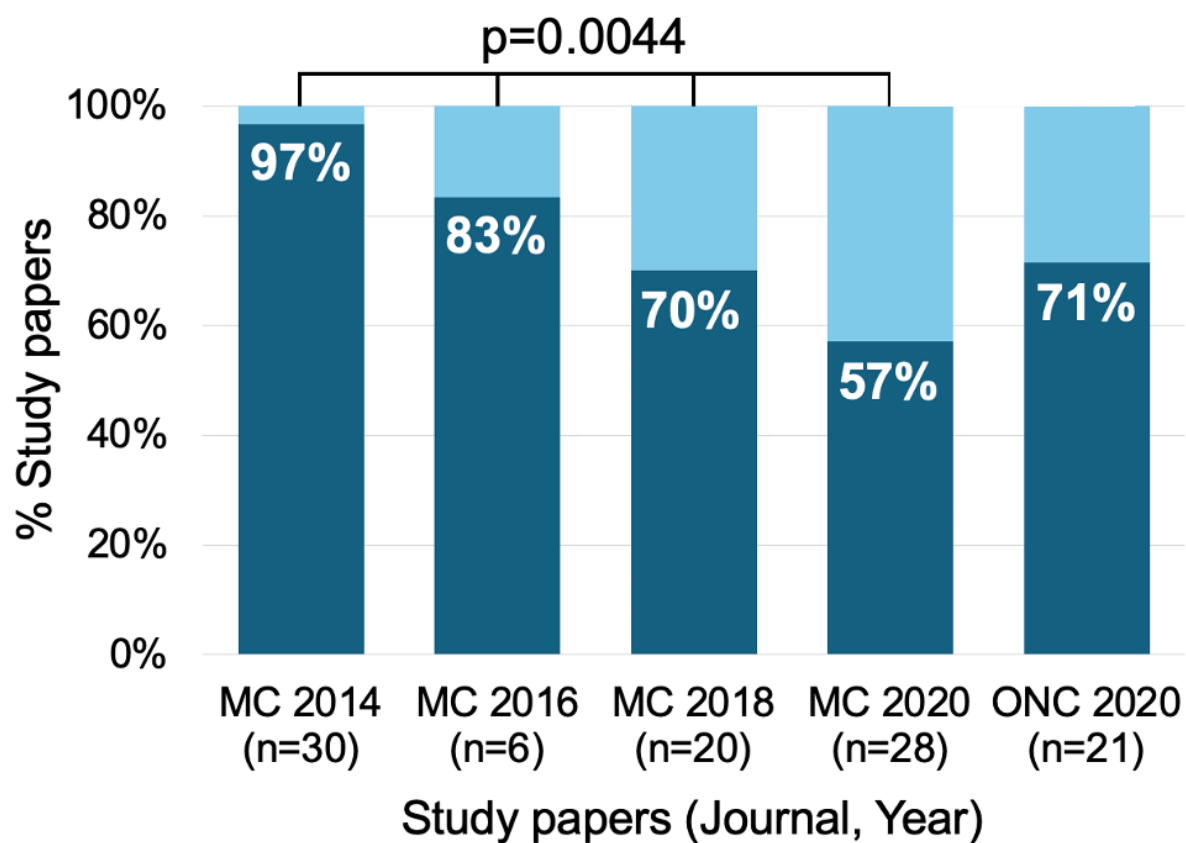


Figure 3.4. Percentage of papers across both arms (Y-axis) that did not receive any author responses on PubPeer (darker shade, percentages shown in white text) according to journal and year of publication (X-axis, journal, year, n=number of papers, MC = *Molecular Cancer*, ONC = *Oncogene*). Chi-Squared Test p-value shown at top.

3.3.4.1 Description of papers with responses

We observed that 28% (15/53) of Arm 1 papers, and 21% (11/52) of Arm 2 papers received a response from authors to our PubPeer queries. Most of these papers were published in 2020 (Arm 1: 9/15, 60%; Arm 2: 8/11, 73%, Figure 3.4). Across the 27 papers with prior PubPeer posts, we observed a significant association where more papers received responses from authors to our queries if they had also responded to prior PubPeer posts (4/4), compared with papers where authors did not respond to prior PubPeer queries (7/23, 30%) (Fisher's Exact Test, $p=0.0188$, $n=27$). However, we did not observe a significant association between whether authors responded to our PubPeer queries and whether the paper had prior PubPeer posts (Fisher's Exact Test, $p=0.2027$, $n=105$).

3.3.4.2 Complete corrections by authors on PubPeer

Approximately 40% (Arm 1: 6/15, 40%; Arm 2: 5/11, 45%) of the papers that received an author response provided new or modified sequences to address all queries posed by our team (Table 3.5). All corrected sequences were independently verified to be correctly identified. For papers allocated to Arm 1, all authors who provided complete corrections responded within the month of the study PubPeer post (Figure 3.5). Similarly, for papers allocated to Arm 2, most authors (3/5) responded within the following month, November 2023 (Figure 3.5). Most papers with complete corrections were published in 2020 (Arm 1: 5/6, Arm 2: 3/5, Figure 3.5, Table 3.5). The remaining three papers (Arm 1: 1/3, Arm 2: 2/3) were published in 2018 (Figure 3.5, Table 3.5). Most authors who provided complete corrections noted the original error(s) to be due to a typographic mistake or copy-paste error during manuscript preparation (Table

3.5). One paper in Arm 1 presented sequence reagents in the incorrect orientation, claiming that the reagents were presented in 5'-3' orientation, despite the sequence being shown in a 3'-5' orientation (Table 3.5, Supplementary Tables 4.1, 4.2).

Three Arm 1 papers and one Arm 2 paper that corrected all sequences on PubPeer (Figure 3.5) stated their intent to seek a correction from the journal's editorial office (Table 3.5). Two other Arm 1 papers that corrected all sequences did not state any intention to seek a correction or comment on the significance of the results (Table 3.5). In contrast, 4 Arm 2 papers did not mention seeking a correction but noted that the corrected errors did not affect the study's key conclusions or results (Table 3.5, Supplementary Table 4.1).

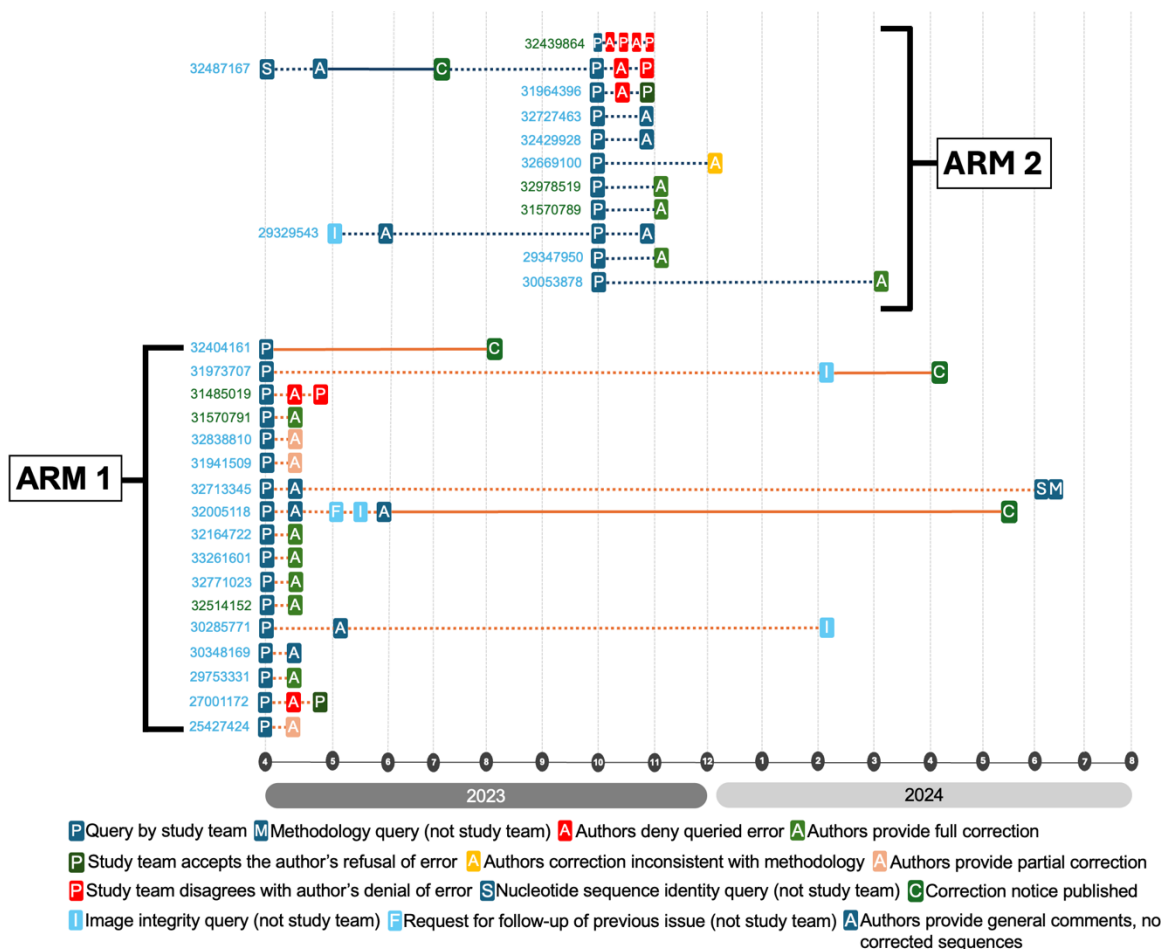


Figure 3.5. Diagrammatic representation of PubPeer posts and journal responses to papers in Arm 1 (orange) and Arm 2 (blue), according to the timeline (X-axis, years, numbers refer to months). Each horizontal line represents a paper denoted by its PMID (green = *Oncogene*, blue = *Molecular Cancer*). Time between PubPeer comments is shown by dashed lines, time between PubPeer posts and journal correction notices are shown as solid lines. Symbols used to represent PubPeer posts and journal responses are shown below the X-axis. The scale of the X-axis is indicative, to permit data representation.

Table 3.5. Summary of author responses that provided new reagent information to completely correct the errors described by the study team, MC = *Molecular Cancer*, ONC = *Oncogene*

Arm	PubMed Identifier (Journal, year)	Claimed identity of corrected reagents (n= no. of reagents)	Type of error queried (reagent type)	Correction by authors	Cause of error according to authors	Author intent to seek correction?
1	29753331 (MC, 2018)	<i>TIGAR</i> (n=2)	Targeting reagents verified to be non-targeting (single sequence reagents)	Provided original sequences in correct orientation	Incorrect sequence orientation	Not stated
1	32514152 (ONC, 2020)	<i>miR-4286</i> (n=1)	Targeting reagent verified to be non-targeting (RT-PCR primer)	Provided the original sequence with mistake corrected	Typographical mistake	Not stated
1	32771023 (MC, 2020)	<i>NFAT1</i> (n=1)	Targeting reagent verified to target another gene (single sequence reagent)	Provided new sequences, verified to be correct	Copy-paste error	Yes
		<i>ATF3</i> (n=1)	Targeting reagent verified to be non-targeting (single sequence reagent)			
1	33261601 (MC, 2020)	<i>MMP3</i> (n=1)	Targeting reagent verified to be non-targeting (RT-PCR primer)	Provided new sequence, verified to be correct	Copy-paste error	Yes
1	32164722 (MC, 2020)	<i>P27</i> (n=1) <i>hsa_circ_0000384</i> , <i>circMRPS35</i> (n=1)	Targeting reagents verified to be non-targeting (RT-PCR primers)	Provided new sequences, verified to be correct	Copy-paste error	Yes
		<i>FOXO3a</i> (n=1)	Targeting reagent verified to be non-targeting (PCR-ChIP primer)			

Table 3.5 cont.

Arm	PubMed Identifier (Journal, year)	Claimed identity of corrected reagents (n= no. of reagents)	Type of error queried (reagent type)	Correction by authors	Cause of error according to authors	Author intent to seek correction?
1	31570791 (ONC, 2020)	<i>miR-9-5p</i> (n=1)	Targeting reagent verified to target another gene (reagent type not stated)	Provided new sequences, verified to be correct	Not stated	Not stated
		<i>hsa_circ_0007874</i> (n=2) <i>hsa_circ_0004913</i> (n=2) <i>hsa_circ_0001946</i> (n=2)	Non-verifiable reagents (single sequence reagent)	Provided new sequence/modified sequence and provided additional detail to claimed identifiers, verified to be correct		
2	30053878 (MC, 2018)	<i>SOX2</i> (n=1) <i>miR-132</i> (n=1)	Targeting reagents verified to target another gene (RT-PCR primers)	Provided new sequences, verified to be correct	Copy-paste error	Not stated
		<i>SOX2</i> (n=1) <i>miR-132</i> (n=1)	Targeting reagents verified to be non-targeting (RT-PCR primers)			
2	29347950 (MC, 2018)	<i>ASMA</i> (n=1) <i>AREG</i> (n=1)	Targeting reagents verified to be non-targeting (RT-PCR primers)	Provided new sequences, verified to be correct	Copy-paste error	Not stated
		<i>WNT1</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)	Linked previously published existing sequence to correct gene identifier.		

Table 3.5 cont.

Arm	PubMed Identifier (Journal, year)	Claimed identity of corrected reagents (n= no. of reagents)	Type of error queried (reagent type)	Correction by authors	Cause of error according to authors	Author intent to seek correction?
2	31570789 (ONC, 2020)	<i>SNAI2</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)	Provided new sequence, verified to be correct	Copy-paste error	Not stated
2	32978519 (ONC, 2020)	<i>LNC-ATP6V0E2</i> (n=2) <i>LINC00294</i> (n=2)	Targeting reagents verified to be non-targeting (RT-PCR primers)	Provided new sequences, verified to be correct	Not stated	Not stated
2	32669100 (MC, 2020)	Non-targeting (n=1)	Invalid negative control reagent (single sequence reagent)	Provided new sequences, verified to be correct	Copy-paste error	Yes
		<i>HNRNPL</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)			

3.3.4.3 Partial corrections by authors on PubPeer

Authors of three Arm 1 papers offered partial corrections through PubPeer within one month of posting the query, where they dismissed some errors while accepting others (Figure 3.5, Table 3.6). For two of these papers, the authors expressed their intention to request a published correction from the journal's editorial office but denied other error claims for different reagents (Table 3.6). We did not agree with these opinions as their explanations did not meet our criteria for verifying these reagents (Table 3.6, Pathmendra et al., 2024; Park et al., 2022). The authors of the third paper did not declare an intention to seek a published correction, but confirmed that, after reviewing the original data, they had used the correct reagents and supported their correction with screenshots of sequence alignments to the claimed target (Table 3.6). They rejected our error claim, citing methylation as the reason for the lack of sequence identity with the claimed target, despite also claiming that the primers in question were designed to amplify 'unmethylated' genes (Table 3.6).

Table 3.6. Summary of author responses that provided partial corrections to errors described by the study team, MC = *Molecular Cancer*.

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error queried (reagent type)	Assertion by study authors	Action taken	Author intent to seek correction?
1	31941509 (MC, 2020)	<i>miR-33a-5p</i> (n=1)	Targeting reagents verified to be non-targeting (forward RT-PCR primer)	Denied error – stated that 10 nucleotides of identity to claimed miRNA is sufficient	No response to authors	No, errors denied
		<i>miR-33a-5p</i> (n=1)	Universal reverse RT-PCR primer claimed to incorrectly target a specific miRNA	Acknowledged queried primer to be a universal primer, but did not accept that this contradicted with claimed identity as a miRNA-specific primer		
		<i>CTNNB1</i> (n=1)	Targeting reagent verified to target another gene (forward RT-PCR primer)	Accepts error originated from typographical error in claimed target gene identifier and mistaken copy-paste of sequence	Authors provided the correct gene identifier and new sequences verified to be correct	Yes

Table 3.6 cont.

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error queried (reagent type)	Assertion by study authors	Action taken	Author intent to seek correction?
1	32838810 (MC, 2020)	hsa_circ_0001445, circSMARCA5 (n=2)	DIG/Biotin probes claimed to target circRNA	Denied claim - theoretical possibility that probe could bind to both linear and circular transcripts was excluded experimentally	No response to authors	No, errors denied
		<i>CDC2</i> (n=2)	Targeting reagents verified to be non-targeting (RT-PCR primers)	Accepted errors, originated from copy-paste errors	Authors provided new sequences, verified to be correct	Yes
1	25427424 (MC, 2014)	<i>SOX1</i> (n=1)	Targeting reagent verified to target another gene (forward RT-PCR primer)	Denied error, stated that primers were used to study methylated transcripts, despite publication claiming primers for unmethylated targets	No response, deny refusal by study authors as the primers were originally claimed as 'unmethylated'	No, errors denied
		<i>SOX1</i> (n=1)	Targeting reagent verified to be non-targeting (reverse RT-PCR primer)			
		<i>SOX1</i> (n=2)	Targeting reagents verified to target another gene (RT-PCR primers)	Accepted errors, originated from copy-paste error	Authors provided new sequences, verified to be correct	Not stated

3.3.4.4 Author responses that denied claimed reagent errors

For 5 queried papers (n=2 Arm 1 papers, n=3 Arm 2 papers), the authors denied all error claims, responding within the month following the post. In most cases (4/5), errors affecting multiple reagents targeting the same gene or RNA were often denied. For two papers, we accepted the authors' explanations and responded on PubPeer, acknowledging our original query as a false positive (Table 3.7). Reasons included human error in interpreting the claimed target species or database and/or algorithm issues that produced incorrect results (Table 3.7). In the cases of two other papers, authors denied errors by stating that they had followed conventional standards. We disagreed, either because authors used unclear nomenclature or inadequate reagent descriptions. In both instances, we responded to the authors, stating that insufficient published information can cause misunderstandings, and explaining that we verified reagent identities using an established protocol (Table 3.7).

In the final example, we questioned a reverse RT-PCR primer claimed to target a specific miRNA but predicted to be a universal primer (Table 3.7). The authors agreed but argued that there is no contradiction between an RT-PCR reverse primer being identified as a universal primer and being claimed to target a specific miRNA (Table 3.7).

Table 3.7. Summary of author responses that denied errors claimed by the study team, MC = *Molecular Cancer*, ONC = *Oncogene*

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error queried (reagent type)	Assertion by study authors	Action taken by study team
1	27001172 (MC, 2016)	<i>Itga6</i> (n=1)	Targeting reagent verified to be non-targeting (PCR-ChIP primer)	Authors stated that primers were used to target mouse gene.	Accepted author explanation on PubPeer, acknowledged false positive result, human error.
		<i>Itga6</i> (n=1)	Targeting reagent verified to target another gene (PCR-ChIP primer)		
1	31485019 (ONC, 2020)	<i>miR-1246</i> (n=1)	Universal reverse RT-PCR primer claimed to target a specific miR	1. Claimed RT/stem loop primer sequence is protected by GenePharma Co., Ltd and cannot be shared. 2. Acknowledged primer to be a universal primer, refused to accept that this contradicts with claimed identity as a miR-specific primer	Refused author's explanation, noted possibility for incorrect primer re-use.
2	31964396 (MC, 2020)	<i>PTBP1</i> (n=2)	Targeting reagents verified to be non-targeting (shRNA)	Showed that reagents target claimed gene (provided screenshot evidence of sequence alignment, including Blastn results)	Accepted author explanation, acknowledged false positive, likely due to database and search algorithms used previously

Table 3.7 cont.

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error queried (reagent type)	Assertion by study authors	Action taken by study team
2	32487167 (MC, 2020)	hg19_circ_0008714 (n=2)	Targeting reagents verified to target another gene (RT-PCR primers)	Denied errors, noting that the predicted target (circCORO1C) was synonymous with the claimed identifier. Claimed identifier was protected (Novogene Co, Ltd) and not publicly available.	Refused author explanation, provided identifier cannot be independently verified, open to misunderstandings when used with circBASE
2	32439864 (ONC, 2020)	<i>IncGCMA</i> (n=1)	Targeting reagent verified to target another gene (siRNA)	Claimed that sequence was in 3'-5' orientation, as per "standard convention"	Refused author explanation, no published disclosure of 3'-5' orientation
		<i>IncGCMA</i> (n=1)	Targeting reagent verified to be non-targeting (siRNA)	Claimed that published sequence was not completely in 5'-3' orientation, where one half of the sequence was noted to be in 3-5' orientation. Authors in follow-up reply provided full shRNA sequence written in 5'-3' orientation	Refused author explanation, no published disclosure of the partial 3'-5' orientation

3.3.4.5 Author responses that did not explicitly address claimed errors

Two *Molecular Cancer* papers (Arms 1 and 2) accepted error claims in general statements, claiming that errors had originated from copy-paste errors during manuscript preparation. However, the authors did not provide new sequences to replace the incorrect sequences (Table 3.8, Figure 3.5). The response to one of these papers described an intent to seek a published correction (Table 3.8). Authors of 4 other *Molecular Cancer* papers (3 Arm 1 papers, one Arm 2 paper) responded within the month of the post or the following month, stating that they would conduct follow-up investigations (Table 3.8, Figure 3.5). Two of these papers also stated that they would seek a published correction if they agreed with our error claims (Table 3.8).

Table 3.8. Summary of author responses that provided neutral comments or incomplete responses to errors described by the study team, MC = *Molecular Cancer*

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error (reagent type)	Did authors accept the error/mention conducting follow-up investigations?	Author intent to seek published correction?
1	30348169 (MC, 2018)	<i>G9a</i> (n=2)	Targeting reagent verified to target another gene (RT-PCR primers)	Accepted errors, did not provide new sequences	Yes
1	32713345 (MC, 2020)	<i>miR-142-3p</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)	Expressed intent to follow-up - "We will further verify and validate the relevant nucleotide sequences in the above"	Not stated
		<i>GAPDH</i> (n=2)	Targeting reagents verified to be non-targeting (RT-PCR primers)		
1	30285771 (MC, 2018)	<i>GAS5</i> (n=2)	Targeting reagents verified to be non-targeting (RT-PCR primers)	"We will check the relevant nucleotide sequences..."	Yes (upon confirming errors)
		<i>Kcnq1ot1</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)		
1	32005118 (MC 2020)	<i>miR-340</i> (n=1)	Targeting reagent verified to target another gene (RT-PCR primer)	"...we will check the primer and probe sequence order immediately"	Not stated
		<i>hsa_circ_001680/B2M</i> (n=1)	circRNA targeting reagent verified to not discriminate between linear and circular transcripts (single sequence reagent)		
		<i>miR-340</i> (n=1)	Targeting reagent verified to be non-targeting (single sequence reagent)		

Table 3.8 cont.

Arm	PubMed Identifier (Journal, year)	Claimed identity of queried reagents (n= no. of reagents)	Type of error (reagent type)	Did authors accept the error/mention conducting follow-up investigations?	Author intent to seek published correction?
2	32727463 (MC, 2020)	<i>c-myc</i> (n=2)	Targeting reagents verified to target another gene (RT-PCR primers)	Accepted errors, did not provide new sequences	Not stated
2	29329543 (MC, 2018)	<i>FOXC2</i> (n=1) <i>GFOD1</i> (n=1) <i>ATG9A</i> (n=1), <i>ATG9B</i> (n=2), <i>PRAS40</i> (n=2)	Targeting reagents verified to target another gene (RT-PCR primers)	“We will contact first authors to check sequences” Authors acknowledged that errors could be due to copy-paste errors during manuscript preparation/false positive observations due to database updates	Yes (upon confirming error in follow-up investigation)
		<i>Raptor</i> (n=1)	Targeting reagent verified to be non-targeting (RT-PCR primer)		

3.3.5 Publisher responses over the study period

3.3.5.1 No responses

As part of the study design, the editors-in-chief of *Molecular Cancer* and *Oncogene* were emailed the list of queried errors on 16 March 2023. The study team received no response from either journal to these emails. Throughout the study period (April 2023 to July 2024), most papers did not receive a post-publication notice (Arm 1: 50/53, 94%; Arm 2: 48/52, 92%). This included n=7 Arm 1 papers and n=3 Arm 2 papers, where the authors had either stated that they would seek a published correction or do so if they agreed with our claim of error upon further investigation (Tables 3.5, 3.6, 3.8). However, no corrections had been published as of July 2024, despite 15 and 9 months passing since our PubPeer posts were made (Arms 1 and 2, respectively).

3.3.5.2 Papers that received post-publication notices during the study

Three Arm 1 papers received corrections that addressed the wrongly identified nucleotide sequence reagents that we queried, where two of these corrections also addressed image integrity concerns that were flagged on PubPeer by others prior to the study (Figure 3.3, Table 3.9). The 3 corrected papers were published in *Molecular Cancer* in 2020 (Figure 3.3, Table 3.9). We have discussed the content of these corrections in detail in Sections 3.3.3.2.1 to 3.3.3.2.3.

One Arm 2 paper received a correction in July 2023 addressing a wrongly identified nucleotide sequence reagent queried by another poster three months earlier on

PubPeer (Figures 3.3, 3.4, Table 3.9). This occurred before our comments on Arm 2 papers were posted in October 2023. The authors responded within one month of our post and denied our error claims (Tables 3.7, 3.9).

Two Arm 2 papers published in *Oncogene* in 2020 were retracted, based on image integrity concerns raised on PubPeer 9 or 22 months earlier (Figure 3.3, Table 3.9, Supplementary Table 4.1). The 2014 *Molecular Cancer* Arm 2 paper was flagged on PubPeer due to image integrity concerns in October 2022, prompting authors to request a correction, where they were unable to provide “suitable data for the corrected image” (PMID 37101172). Consequently, the editor published an expression of concern, 6 months after image integrity concerns were flagged on PubPeer in April 2023. No publication notices for Arm 2 addressed our concerns, despite our email sent to the editors before notices were published (Table 3.9 Supplementary Table 4.1).

Table 3.9. Summary of post-publication notices published during the study. Asterisks represent papers with prior correction, MC = *Molecular Cancer*, ONC = *Oncogene*

Arm	PubMed Identifier (Journal, year)	Type of post-publication notice (PubMed Identifier, month, year)	Type of error queried by our team (reagent type, gene, n= no. of reagents)	Were these queries addressed (time between PubPeer query editorial notice)	Other errors addressed in notice and corresponding PubPeer activity if any
1	32404161* (MC, 2020)	Correction (37598189, August 2023)	Targeting reagents verified to target another gene (RT-PCR primers, <i>BIM</i> , n=2)	Provided new RT-PCR primer sequences verified to be correctly identified, claim to have redone the experiment and produced results consistent with claims in original paper (April-August 2023) Provided correctly identified sequences of RT-PCR primers claimed to target B-actin, not disclosed in original publication	None
1	31973707 (MC, 2020)	Correction (38566109, April 2024)	Targeting reagents verified to target another gene (RT-PCR, <i>circPTK2</i> , n=2)	Provided new primer sequences verified to be correctly identified (April 2023 – April 2024). Error was also queried by another poster (March 2022)	Provide corrected image Fig 4D, flagged on PubPeer for image overlap (February-April 2024)

Table 3.9 cont.

Arm	PubMed Identifier (Journal, year)	Type of post-publication notice (PubMed Identifier, month, year)	Type of error queried by our team (reagent type, gene, n= no. of reagents)	Were these queries addressed (time between PubPeer query editorial notice)	Other errors addressed in notice and corresponding PubPeer activity if any
1	32005118 (MC, 2020)	Correction (38741180, May 2024)	Targeting reagent verified to target another gene (RT-PCR primer, <i>miR-340</i> , n=1)	Provided new sequence and disclosed the identity of universal primer, predicted to potentially produce primer dimer.	Provide corrected image Fig 2H, flagged on PubPeer for image similarity (February 2020-May 2024), Fig 3I and 3L, flagged on PubPeer for image overlap, Figure S2, flagged on PubPeer for duplication (May 2023-May 2024) Elisabeth Bik reminded authors about seeking correction for previously flagged errors in May 2023
			circRNA targeting reagent verified to not discriminate between linear and circular transcripts (single sequence reagent, <i>hsa_circ_001680/B2M</i> , n=1))	Provided new sequences that were verified to be correctly identified (April 2023-May 2024)	
			Targeting reagent verified to be non-targeting (single sequence reagent, <i>miR-340</i> , n=1)		
2	32487167* (MC, 2020)	Correction (37438789, July 2023)	Targeting reagents verified to target another gene (RT-PCR primers, <i>hg19_circ_0008714</i> , n=2)	No, the correction was published before PubPeer post in October 2023 and authors denied error claim	Corrected typographical mistake in <i>let-7c-5p</i> RT-PCR forward primer by providing new sequence in supplementary file, matching the sequence of <i>let-7c-5p</i> the authors disclosed in figure 3C and 6I (April-July 2023)

Table 3.9 cont.

Arm	PubMed Identifier (Journal, year)	Type of post-publication notice (PubMed Identifier, month, year)	Type of error queried by our team (reagent type, gene, n= no. of reagents)	Were these queries addressed (time between PubPeer query editorial notice)	Other errors addressed in notice and corresponding PubPeer activity if any
2	25193015 (MC, 2014)	Editorial expression of concern (37101172, April 2023)	Targeting reagent verified to be non-targeting (RT-PCR primer, <i>let-7d</i> , n=1)	No, the expression of concern was published before PubPeer post in October 2023 and authors did not respond on PubPeer	Authors attempted correct Figure 2e and 6f flagged on PubPeer for image overlap, but unable to provide data for the corrected image (October 2022-April 2023)
2	33122828 (ONC, 2020)	Retraction (37253965, May 2023)	Targeting reagents verified to be non-targeting (RT-PCR primers, <i>miR-139-5p</i> , n=2)	No, the paper was retracted before PubPeer post in October 2023 and authors did not respond on PubPeer Concern about the identity of PRC1 also raised by another poster in June, 2021	Editor-in-Chief retracted the paper for image integrity concern flagged on PubPeer, where an identical, scratched ruler has appeared in figures across multiple articles (July 2021-May 2023)
			Targeting reagents verified to target another gene (RT-PCR primers, <i>PRC1</i> , n=2)		
2	33273726 (ONC, 2020)	Retraction (37420031, July 2023)	Targeting reagents verified to target another gene (RT-PCR primers, <i>ATG10</i> , n=1, <i>HuR</i> , n=1)	No, the paper was retracted before PubPeer post in October 2023 and authors did not respond on PubPeer	Editor-in-Chief retracted the paper for image overlap in Figure 4H and 7D with figures from published articles flagged on PubPeer (October 2022-July 2023)
			Targeting reagents verified to be non-targeting (RT-PCR primers, <i>ATG10</i> , n=1, <i>HuR</i> , n=1)		

3.3.5.2.1 Correction – PMID 38566109

PMID 31973707 was issued a correction (PMID 38566109) for the reagent error we identified, which was also flagged by another PubPeer user 13 months earlier (Figure 3.3, Table 3.9). Ten months after our PubPeer post, an anonymous user raised an image integrity concern about Figure 4D in February 2024 (Figures 3.2, 3.4, Table 3.9). A correction addressing both issues was published in April 2024. This means that 25 months (overlapping with the study period) were required for the correction to be published (Figure 3.3, 3.4, Table 3.9). The authors did not respond to any PubPeer posts during this time and did not reference PubPeer comments in the published correction. We verified that the new primer sequences were correctly identified (Table 3.9, Supplementary Table 4.2).

3.3.5.2.2 Questionable correction – PMID 37598189

The correction notice to PMID 32404161 was published four months after our PubPeer post (Figure 3.5, Table 3.9), with no reference to our PubPeer comment. The authors also did not respond to our query on PubPeer (Figure 3.5). The authors described using RT-PCR to measure *BIM* expression across the lung adenocarcinoma cell line NCI-H1975 and its ASK120067/Limertinib (*EGFR* inhibitor) resistant counterpart (PMID 32404161). However, we verified that these primers were wrongly identified and predicted to target *CDH10*, an unrelated gene (Table 3.9, Supplementary Table 4.2).

In the correction, the authors addressed the reagent errors that we described, claiming “authors do notice that they mis-claimed the qRT-PCR primers”. The authors stated

that they had conducted the experiments using redesigned primers and obtained similar results to those of the initial study, therefore, asserting that these mistakes do “not affect their critical conclusions” (PMID 37598189). We verified that the new primer sequences were correctly identified (Table 3.9, Supplementary Table 4.2). The authors noted that they “observed the similar results as our previous data, which was also consistent with the protein levels of *BIM* previously determined” (PMID 37598189). However, no biological explanation was given for the similar results obtained for these different gene targets (*BIM* versus *CDH10*).

3.3.5.2.3 Incorrect correction – PMID 38741180

The correction notice (PMID 38741180) for PMID 32005118 was published 13 months after our PubPeer post, where the authors had responded on PubPeer within the month of our post (Figure 3.5). 38 months (3 years, 2 months) before our post, Dr Elisabeth Bik had raised image integrity concerns on PubPeer in February 2020 (Figure 3.3, Table 3.9). The authors replied, acknowledged the error and stated, “I will contact the editor to solve the problem immediately” (Table 3.8, 3.9). No correction was published at this point. In the month after our post in April 2023, Dr Bik questioned whether the authors had sought a published correction (Figure 3.5, Table 3.9). Dr Bik also identified additional image integrity concerns, to which the authors responded, “We will send an email to the editor as soon as possible”. A correction was finally published one year after this reply, in May 2024 (Table 2.9). The time to correction from the earliest PubPeer post describing an image integrity concern that was addressed in the notice was 51 months (4 years, 3 months), which overlapped with our study.

We identified three wrongly identified nucleotide sequence reagents that the authors corrected by providing new sequences (Table 3.9). In the correction notice (PMID 38741180), the authors provided new sequences and did not disclose the reason for the errors. In an earlier PubPeer response to Dr Bik's earlier post in February 2020 they stated "We put this result in supplemental figure 2. Reviewer advice we put this result in figure 2. We made the mistake when we rearranged these results". Independent verification showed that the new sequences provided to correct the queried errors were correctly identified (Table 3.9, Supplementary Table 4.2). However, in this correction, the authors also disclosed the identity of the universal, reverse RT-PCR primer that worked in tandem with the forward primer (which we previously queried) (Table 3.9). Verification revealed that forward and reverse RT-PCR primers share eight nucleotides of reverse complementarity (Figure 3.6). This suggests the primers could bind to each other, leading to amplification of a dimer in addition to *miR-340*. In the correction (PMID 38741180), the authors claimed that these errors did not impact the interpretation of the main results and conclusions. However, these primers may not efficiently amplify *miR-340*, which was stated to be regulated by *hsa_circ_001680* and a regulator of colorectal cancer chemoresistance (PMID 32005118).

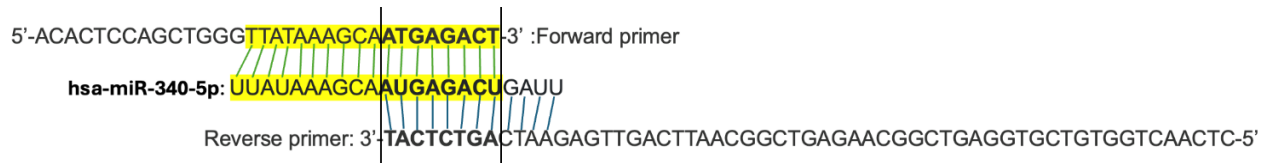


Figure 3.6. Alignment of forward and reverse RT-PCR primers provided in PMID 38741180 and miR-340-5p sequence sourced from miRbase (Griffiths-Jones et al. 2006). Regions matching the miRNA transcript and the forward primer are highlighted in yellow. Green lines indicate matching nucleotides. Bold sequences show nucleotides shared/complementary between forward, reverse, and miRNA sequences. Blue lines show sequence complementarity.

3.4 Discussion

3.4.1 Summary of results

In this study, we studied whether posting comments on PubPeer prompts editorial action. On March 16, 2023, we emailed the editors-in-chief of *Molecular Cancer* and *Oncogene* about a total of 105 papers that reported 273 incorrectly identified nucleotide sequence reagents (Table 3.2). Neither editor responded to these emails. Prior to this study, we had also discussed our results with the same editor-in-chief of *Molecular Cancer* in general terms without referring to specific papers.

We then divided the papers into two arms: Error notices for Arm 1 papers were posted on PubPeer in April 2023, and notices for Arm 2 papers were posted 6 months later. If PubPeer posts influenced editorial responses, we expected to see post-publication notices (corrections, retractions, or expressions of concern) following the PubPeer posts, where for Arm 2 papers, notices might be published after our PubPeer posts (October 2023) (Figure 3.1). We decided on a 6-month interval between the posts for Arms 1 and 2 as this was workable within the requirements of PhD candidature.

Most error descriptions on PubPeer received no responses from authors (79/105, 75%, Section 3.3.4), with a higher proportion of 2014 papers not receiving responses from authors compared with papers published in later years (Figure 3.4). Conversely, most papers with author responses on PubPeer were published in 2020 (Arm 1: 9/15, 60%; Arm 2: 8/11, 73%, Figure 3.4, Section 3.3.4.1). These response rates are higher than those described by Ortega et al. (2021). We observed that most authors

responded within 1-2 months following our post, an observation consistent with author responses to posts made prior to the study (Figure 3.3). In line with expectations, we also observed that authors who had responded to prior PubPeer posts were also more likely to respond to our PubPeer posts (Section 3.3.4.1).

Some (n=14) author responses provided at least one new sequence to correct errors (Figure 3.5, Tables 3.5, 3.6), followed by a further 7 papers that provided more general responses, noting the intent to carry out follow-up investigations or acknowledging the nucleotide sequences as wrongly identified (Table 3.8). Authors of eight papers disagreed with our descriptions of wrongly identified nucleotide sequence reagents (Table 3.7), where authors of three papers provided corrections for some queried reagents, whilst disagreeing with other claimed errors (Table 3.6). Two author disagreements (Table 3.7) were accepted as corrected, stemming from either our misinterpretation of the claimed identity of reagents, or possibly due to false negative Blastn results (Bazinet et al. 2018; Koonin and Galperin, 2003). For the 8 papers where we disagreed with the author's denial of our claimed errors, reasons included a lack of information that the authors later added via the PubPeer responses, or use of identifiers and terminology that were contradictory with established knowledge or susceptible to misinterpretation by a broad readership (Table 3.6, 3.7).

Prior to the study, a small proportion (14/105, 13%) of papers had an associated correction, mostly addressing errors, predominantly related to image integrity concerns noted on PubPeer by others (Figure 3.3, Section 3.3.3). Some 13 papers with PubPeer comments posted by others prior to the study have yet to be addressed

via a published correction. Similarly, we observed a low journal response rate across both arms during the study, with only 7 papers receiving a post-publication correction. This was especially surprising as 10 papers with author responses noted their intent to seek a correction; however, none of the authors of these papers had published a correction as of July 2024 (Section 3.3.5). The low rate of published corrections addressing our errors (Figures 3.2, 3.4) highlights inefficiencies in post-publication corrections. Most PubPeer notices describing incorrect or NV nucleotide sequence reagents did not result in any post-publication notices, indicating that PubPeer discussions have limited impact on post-publication journal responses.

In saying this, a small number of papers with incorrect reagents were appropriately addressed by post-publication corrections. Three corrections of *Molecular Cancer* 2020 papers addressed the errors that we queried, at four, 10, and 13 months after our PubPeer posts, respectively (Section 3.3.5, Table 3.9). For one other Arm 2 paper, the authors published a correction addressing a reagent error identified by others, while denying our error claim (Figures 3.2, 3.4, Table 3.9). Furthermore, two Arm 2 *Oncogene* papers were retracted, and one Arm 2 *Molecular Cancer* paper had an expression of concern issued prior to our PubPeer post in October 2023. Neither the retraction notices nor the expression of concern cited the errors that we have identified, despite emailing the editor in March 2023 and only referred to image integrity concerns flagged by others on PubPeer (Figure 3.3, Table 3.9, Section 3.3.5). Overall, this suggests that PubPeer posts could lead to post-publication correction in rare cases, but that responses are insufficient compared with the scale of errors present in the literature.

3.4.2 Limitations of the study

Before interpreting these results, we must acknowledge several limitations of our study. Firstly, the generalisability of our findings is limited by having studied two journals, *Molecular Cancer* and *Oncogene*, from the same publisher, Springer Nature. Another limitation is that we only reported errors in nucleotide sequence reagent identities. As described by Ortega et al. (2021), image integrity concerns dominate PubPeer posts. As shown by the cases where authors refused our error claims (Table 3.7), there may be a lack of understanding of nucleotide sequence reagents, which could partly explain the response rates we observed. Given that previous studies have noted that publication of post-publication corrections can take several years (Byrne et al., 2021; Ortega, 2021), our study period of 15 months (April 2023 - July 2024) and the six-month gap between Arms 1 and 2 may have been insufficient to capture all publisher responses.

Nevertheless, extending the study period might have confounded the research in two ways. Firstly, as original studies age, they may become less likely to receive responses from authors on PubPeer or from journal editors. In this study, more papers published in 2020 received author responses compared to those published in 2014 (Figure 3.4, Section 3.3.4). Secondly, a longer study period could increase the chance that papers will attract PubPeer comments from others, which could further motivate authors to correct or update their papers. However, we found no evidence supporting this, as we did not observe an association between whether a paper had prior PubPeer comments and whether authors responded to our PubPeer posts (Section 3.3.4.1, Supplementary Table 4.1). Instead, we observed that authors who responded to prior

posts generally responded to our PubPeer posts, suggesting that if authors do respond, they will continue to do so (Section 3.3.4.1, Supplementary Table 4.1).

As mentioned earlier, we had been in communication with the *Molecular Cancer* and *Oncogene* editors-in-chief prior to the study, and hence, both journals had been aware of our concerns for a longer period than the study timeframe. We believe the 15-month observation period during the study was adequate, and we had reasonable expectations that journals could publish corrections within six months, since the errors had also been shared on PubPeer.

3.4.3 Possible causes of low response rates

The low response rates on PubPeer, coupled with even lower response rates in terms of post-publication editorial notices during the study period, highlight challenges of correcting the scientific record (Bolland et al., 2021; Byrne and Barnett, 2024; Ortega, 2021; Ortega and Delgado-Quirós, 2023). As Byrne et al. (2021) noted, the time to publish a correction for misidentified nucleotide sequence reagents ranged from 19 to 28 months, whereas the present study included follow-up periods of 15 and 9 months, respectively. No papers where authors had stated an intention to seek a correction had been corrected by the study end. The fact that 15 and 9 months are insufficient to correct errors in publications in two high-impact-factor journals reflects serious failings.

Authors of six papers (Tables 3.5-3.8, Supplementary Table 4.1) stated that nucleotide sequence errors that we described were unlikely to impact key results and

conclusions. This is concerning as it suggests that authors do not recognise the importance of conducting experiments with correct reagents. As described in Pathmendra et al. (2024), some papers published in *Molecular Cancer* and *Oncogene* in 2020 with incorrectly identified nucleotide sequence reagents were highly cited—at least 50 or 100 times—by January 2023, a period of approximately two years. Overall, this presents a worrying picture, where papers describing incorrect reagents are highly cited within a short time frame, yet there is a lack of prompt post-publication corrections to address these errors.

Another explanation for low response rates on PubPeer could be that authors are unaware of PubPeer queries. As noted in Ortega (2021), 8.0% of papers with PubPeer comments about data and image manipulation published before January 2020 received a response from the authors. All papers in our current cohort had a linked email address recognised by PubPeer, so all authors should have received an email as soon as queries were posted (Caron et al., 2024; Stell, 2016). However, as researchers may move between different affiliations, some email addresses could have become outdated (Rodriguez-Esteban et al., 2022). In comparison to Ortega (2021), we observed a 25% author response rate on PubPeer. This could be explained by the recent efforts of indexing services like Zotero (Joshi and Minirani, 2024; Zotero, 2013) that have included PubPeer comments in their monitoring systems, enhancing the possibility of authors being notified or traced.

3.4.4 The implications and significance of discourse on PubPeer

The open discourse on PubPeer between authors and readers also highlights critical misinterpretations within the field of molecular oncology. For instance, we queried two papers studying circRNA, where the authors denied our claims that circRNA reagents were incorrectly identified. In PMID 32487167, the authors used a publicly unavailable circRNA ID that could be misinterpreted through the use of databases such as circBASE, leading to a conflict in interpreting the claimed identity. Another point of disagreement arose when authors refused to accept claimed errors where reverse RT-PCR primers were claimed to target a specific miRNA but were predicted to be universal primers (PMID 31941509 and 31485019, Tables 3.6, 3.7). Such inconsistencies risk misinterpretation and misuse by future researchers (Byrne et al., 2022; Pathmendra et al., 2024).

Alongside incorrectly identified nucleotide sequence reagents, we also examined NV reagents used for circRNA targeting. Authors of one paper (PMID 31570791) responded on PubPeer with corrected sequences. Notably, the authors provided what they claimed was a new targeting sequence for hsa_circ_0007874, which was identical to the original sequence, with only a few nucleotides removed from the 5' and 3' ends (Table 3.5, Supplementary Table, 4.2). The authors did not clearly report the circRNA reagent in the original publication, until we queried the reagents on PubPeer.

The exchanges on PubPeer highlighted the lack of standardisation in some microRNA and circRNA research. Publishers and journals, such as, *Molecular Cancer* and *Oncogene*, are in a position to enforce standards and offer guidance for transparent and accurate reporting. Therefore, both researchers and journals need to follow standards such as the MIQE guidelines for reporting PCR experiments (Bustin et al., 2009), recommendations for accurate reporting of circRNAs (Section 2.4) (Chen et al., 2023; Costa and Enguita, 2020, Pathmendra et al., 2024) or the REAPPRAISE checklist for assessing publication integrity (Grey et al. 2020).

3.4.5 Case studies of corrections

As noted in Byrne et al. (2021), some authors published corrections that seem implausible or are factually incorrect. Here, we describe two of the three published corrections that addressed our concerns but that we evaluated as implausible or potentially incorrect. The cases highlight the need for more scrutiny and critical evaluation of corrections before they are published.

One questionable correction concerns PMID 37598189, where the authors initially assessed the relative expression of *BIM* (PMID 32404161), a pro-apoptotic protein also known as *BCL2L11*, downregulated in *EGFR*-resistant lung cancers (Stewart et al. 2015). However, the claimed *BIM* RT-PCR primers were predicted to target *CDH10*. In the published correction (PMID 32404161), the authors stated that they had repeated these experiments using new RT-PCR primers verified to target *BIM* and obtained similar results (Section 3.3.5.2.2). Nonetheless, comparing the corrected and original figures reveals a significant reduction in the reported relative fold change from

the authors' likely measurement of *CDH10* in the original study (PMID 37598189) to their measurement of BIM in the published correction (PMID 32404161). Furthermore, this correction was published at the authors' request (PMID 32404161), yet the correction did not mention *CDH10* or provide a rationale for observing similar results despite measuring a wrong gene.

The second case of a questionable correction is associated with the study (PMID 32005118), the authors state they used RT-PCR to measure *miR-340* expression in colorectal cells, aiming to understand how *hsa_circ_001680* influences colorectal cancer cell proliferation by regulating *BMI1* through *miR-340*. However, verification of the forward and reverse RT-PCR primers claimed to target *miR-340* in the published correction showed 8 nucleotides of reverse complementarity, potentially forming a dimer (Figure 3.6, Table 3.9, PMID 32005118). The authors claim in the correction that the errors will not impact the interpretation of the key results and conclusions; however, the use of these primers, which can form a dimer, would not efficiently amplify the target *miR-340*. The fact that neither editors nor authors have addressed this within the correction highlights a lack of critical evaluation. Both questionable aspects of published corrections prompt us to question whether editors should enforce more rigorous assessment of corrections made by authors in response to queried errors.

3.4.6 Future steps

One would expect that the increasing awareness of PubPeer across the research community would provoke more open discourse on integrity, but this was not the case,

as demonstrated in the present study. The most cited reason for incorrect nucleotide sequence reagent was a copy-paste error, where the authors mistakenly edited or copied and pasted the wrong sequence during manuscript preparation (Tables 3.5, 3.6, 3.8). Such errors should be easily addressed via a published correction; however, this was not the case, given that we had only three published corrections during the study period across the 105 papers that were queried. Follow-up observations at later dates to examine whether other authors have responded or the publisher has issued post-publication notices will strengthen the study and help us to understand whether such easily correctable errors persist in the literature.

There is no doubt that journals and publishers, by extension, hold significant power within the scientific enterprise, as they publish papers that serve as the currency for career progression (Anderson et al., 2007; Fogarty, 2009; Yi et al., 2019). Yet, we saw an alarmingly high number of papers that had not published corrections addressing our queries on PubPeer, suggesting that the actions taken by journals and publishers do not address the integrity issues facing some parts of the scientific record. Caron et al. (2024) claimed that posts on platforms like PubPeer have led to increased workloads within institutions receiving federal research funding, where staff are under extreme pressure. Yet, the current level of inaction is dangerous, as unreliable and incorrect papers not only waste research funds (Freedman et al., 2015) and time but can also mislead future scientific research and undermine public trust in science (Byrne et al., 2022). Publishers need to implement quicker procedures for resolving post-publication queries. Incorrect and implausible corrections highlight the need to critically evaluate corrections before they are published. We have outlined a series of

simple questions that researchers and editors can use to assess published corrections in Table 3.10.

In line with recommendations made in Byrne and Barnett (2024), allowing PubPeer posts to be transferred and linked to original articles, or the development of commenting functions within commonly used search engines or databases like PubMed would be crucial in bridging the current disconnect. We recognise that PubPeer has created a free web browser plugin that allows individuals to easily view an associated PubPeer thread for any article they encounter (Barbour and Stell, 2020). However, this requires individuals to actively install this plugin onto their browser. Based on the lack of response from authors and minimal discourse across most papers, we speculate that a large proportion of the scientific community might be unaware of PubPeer or this plugin. We are also aware that PubMed Commons, a post-publication commenting platform on PubMed was terminated in 2018 citing low user engagement (Byrne and Barnett, 2024; Dolgin, 2018). Given that PubMed is the largest collection of papers accessible to most researchers (National Library of Medicine, 2025), reactivating this related platform could help more researchers become aware of unreliable publications independently of journals. Whilst we recognise the potential for these platforms to be misused, with well-funded and developed moderation systems, we believe that expanded post-publication commentary platforms, combined with researcher awareness, would be vital in ensuring that we can better correct the scientific record.

Table 3.10. Questions to evaluate published corrections

	Questions
Who	<ul style="list-style-type: none"> • Does the correction state who initiated the correction? • Who originally identified the errors? <ul style="list-style-type: none"> - If this was someone other than the authors, how were the authors notified of the error? - Are there additional queries that authors do not address? Is this acceptable? - If the error is methodological, have the authors clarified where the responsibility lies, i.e. authors, company from which the materials or results were sourced, journal?
What	<ul style="list-style-type: none"> • What is the error that authors aim to correct? <ul style="list-style-type: none"> - Is this an error in methodology, representation of results or interpretation in the discussion? • What evidence or explanation do authors provide that justifies that the correction resolves the error, and does not affect the key conclusions of the paper?
When	<ul style="list-style-type: none"> • When were the errors noticed? <ul style="list-style-type: none"> - Do authors state an explanation for why significant time elapsed between when the errors were found and publication of the correction?
Where	<ul style="list-style-type: none"> • Where is the error relative to the key results and conclusions? • What proportion of the article is edited through the correction? Is the correction such that most of the article is edited or affected (including any prior published corrections)?
Why	<ul style="list-style-type: none"> • Is there an explanation for why this error not noticed in pre-publication review by editors, peer reviewers or authors? • Did the authors explain why the error(s) occurred?
How	<ul style="list-style-type: none"> • How have the authors addressed the error? <ul style="list-style-type: none"> - Were the corrections plausible, accurate and/or consistent with existing methodology and knowledge? - Did authors re-conduct their experiments to produce new results, and if so, have they explained the differences and similarities of the new corrected results to the original study?

3.4.7 Summary and Conclusion

In summary, there is a clear disconnect between PubPeer and post-publication action issued by a journal for most articles. Most PubPeer posts were not directly translated into post-publication notices; among the few that had published corrections, some were questionable or incorrect. The development of platforms like PubPeer is only a part of the solution to the problem of published errors and poor publication integrity. There is a clear need for publishers to act upon queries within reasonable timeframes. It is only through prompt and accurate post-publication response to erroneous papers that science can remain accurate and reliable.

Chapter 4: Awareness and experiences of publication integrity from the perspectives of ECRs and post-graduate research students

4.1 Introduction

Scientific publications are intended to facilitate the sharing of ideas. However, the increasing commercialisation of scientific publishing, combined with hypercompetitive environments where researchers are expected to ‘publish or perish’, has led to publications being treated as the currency of research career progression (Anderson et al., 2007; Haven et al., 2019a; Yi et al., 2019). Hypercompetitive research environments are associated with reduced job satisfaction (Christian et al., 2021) and can be conducive to research misconduct (Boulbes et al., 2019; de Vries et al., 2006; Haven et al., 2019a, 2019b; Krstić, 2015; Ljubenković et al., 2021; Mabou-Tagne et al., 2020). Researchers have been known to unconsciously or consciously “spin” their study findings (Boulbes et al., 2018; Boutron & Ravaud, 2018) or fabricate, falsify or omit contradicting data if they believe their overall conclusions to be correct (Hofmann et al., 2020). In severe cases, researchers can resort to organisations known as paper mills that systematically produce manuscripts that authors can use to bolster their academic record (Byrne et al., 2022). This aligns with the increase in retractions of literature, with the primary reason for retraction being scientific misconduct (Chen et al. 2018; Gaudino et al. 2021). However, as evident in Chapter 3, there is a limited capacity for researchers and publishers to flag and correct unreliable research

publications (Byrne et al. 2021; Ortega and Delgado-Quirós, 2023). Unreliable research publications that persist within the scientific record without correction can continue to be used by other researchers, and hence, the scientific literature represents an increasingly unsafe workplace (Byrne and Barnett, 2024).

Postgraduate research students and ECRs are at critical stages of their research careers, where training in research integrity has been shown to help foster ethical research practices (Abdi et al. 2021a; Nicholas et al. 2019). However, hypercompetitive research environments can encourage students and ECRs to publish for career progression, where some may resort to misconduct (Christian et al. 2021). Together, this suggests that while postgraduate research students and ECRs represent researcher groups where interventions can be used effectively to foster research integrity, they are also subject to negative pressures that can make them susceptible to research misconduct and unethical research practices. Survey results also suggest that ECRs may place more emphasis on IF and citations as proxy measures for research quality (Nicholas et al. 2017; Tenopir et al. 2016), when it has been well documented that such measures can be inflated or manipulated (Shanta et al. 2013; Siler and Larivière, 2022). Several studies have also noted the presence of unreliable publications in journals with high IF or with high citation numbers (Craig et al., 2020; Pathmendra et al., 2024; Shema et al., 2019). This suggests that postgraduate research students and ECRs may be more vulnerable to unreliable publications than more experienced researchers.

For the present study, we define publication integrity as the reliability and validity of the literature, such that one can confidently trust the described methods and findings.

The notion of researchers being impacted by poor publication integrity was discussed by Schmidt (2021). This book describes a series of interviews with principal investigators (PIs) in biomedicine, where one topic discussed was irreproducible published results and their impacts on researchers. Most (85%) of PIs answered “yes/definitely/of course/absolutely” to whether irreproducible research results are concerning, with opinions varying (between 30% to 80%) in terms of how much of the literature they perceived to be irreproducible. PIs also collectively reported numerous impacts of irreproducible research results, including personal feelings of frustration, wasting of time, money and resources, and erosion of public trust (Schmidt, 2021). Anecdotally, in Schmidt (2021), a PI reported how at a younger stage of their career, they were easily convinced that it was their fault if they could not reproduce a finding. Another PI reported losing a PhD student throughout their experience with irreproducible research results (Schmidt, 2021).

To our knowledge, there have been few investigations, such as that of Schmidt (2021), that have examined ECR and/or postgraduate student awareness and experiences with publication integrity. A study by Hofmann et al. (2020) surveyed PhD students across three Scandinavian universities to examine their experiences and attitudes toward research misconduct. Although the study did not explicitly focus on the integrity of existing literature, as in Schmidt (2021), it included several questions where participants were asked to respond to statements about their perception of research misconduct in their field (Hofmann et al., 2020). It was noted that 7.8%-12.7% of the PhD student cohort responded with “strongly agree” or “agree” to the statement about fabrication, falsification, or plagiarism being common in their academic discipline

(Hofmann et al., 2020). The study did not further investigate how unreliable publications impacted their careers or personal well-being (Hofmann et al., 2020).

Surveys have consistently reported that ECRs and postgraduate students can engage in research misconduct and poor behaviours that damage publication integrity (Hofmann et al., 2020; Krstić, 2015; Tjink et al., 2014). Consequently, several articles have described the need to teach and provide better role models of integrity to foster an environment of good publication integrity for ECRs and postgraduate students (Abdi et al., 2021a; Hofmann et al., 2020; Young and Mitterboeck, 2020). A more recent study by Lubega et al (2023) noted that biomedical science graduates are likely to be biased towards interpreting failures to replicate as a lack of skill on their part, which can perpetuate negative feelings of anxiety or depression. Whilst these results hint at possibly similar ECR and research student experiences to those described by Schmidt (2021), Lubega et al. (2023) focused solely on reproducibility. The study (Lubega et al., 2023) thus cannot be used to assess the impacts and awareness of poor publication integrity more broadly. As such, the perspectives, understanding, and experiences of ECRs and research students regarding publication integrity remain largely unknown. To address this gap, our present qualitative survey aims to identify information about the awareness, experiences and impacts of poor publication integrity as described by postgraduate research students and ECRs.

4.2 Methods

This study was approved by the University of Sydney's Human Research Ethics Committee [Project Number: 2023/739]. Our analysis draws on well-established qualitative research traditions, including empirical phenomenology (Eberle, 2014; Karlsson, 1993) and grounded theory (Charmaz, 2014). In empirical phenomenology, the researcher analyses participant descriptions of thoughts, feelings, attitudes and notions about a particular phenomenon to generate "the logos of the phenomenon, that is to say those necessary constituents (structure) which are needed for just that particular phenomenon to be what it is" (Karlsson, 1996; Mortari et al., 2023). Our empirical work employed qualitative survey methods informed by constructed grounded theory (Charmaz, 2014), aiming to develop a theoretical understanding of how participants navigate the literature in terms of publication integrity based on their self-reported personal experiences. Such methods are well-suited for understanding the attitudes, experiences, and processes that underpin how individuals navigate a particular phenomenon (Charmaz, 2014; Karlsson, 1996; Mortari et al., 2023). Hence, through these methods, we addressed our aim of developing a theoretical understanding of how ECRs and postgraduate research students navigate publication integrity in both educational and research contexts. The study adhered to the ICC/ESOMAR International Code on Market, Opinion and Social Research and Data Analytics (ICC/ESOMAR, 2016) to ensure safe and ethical practice and results were reported according to the Checklist for Reporting Results of Internet E-surveys (CHERRIES) (Eysenbach, 2004).

4.2.1 Author experience and reflexivity

Researchers with diverse disciplinary backgrounds in molecular biology, statistics and meta-research supported the study. All authors have worked in some capacity within publication integrity or conducted qualitative research, where they have previously worked in evaluating the literature and publishing practices of their respective disciplines (PP, JAB and AGB, as per acknowledgements) or qualitatively examined the researchers' experiences with poor quality research literature (BZS, as per acknowledgements). The primary investigator (PP) also completed coursework on qualitative research methodology as part of his doctoral candidature, which underpins the method of this chapter.

4.2.2 Survey Design

Interviews and focus groups are commonly employed in phenomenological studies, as their formats facilitate more in-depth responses (Mortari et al., 2023). However, we adopted an online anonymous survey due to limited resources and time. Additionally, anonymous surveys encourage participants to candidly discuss their experiences (Murdoch et al., 2014). They are therefore suitable for discussing publication integrity (including subjects such as fraud and personal impacts) that they might not be comfortable discussing in an identifiable setting. Online surveys also enable a more diverse participant population (Regmi et al., 2016).

To our knowledge, no qualitative survey of postgraduate students and ECRs knowledge and experience of publication integrity has been previously conducted.

Hence, all topic questions were designed by the team, while demographic questions were based on the survey by Christian et al. (2021). Overall, the survey consisted of 6 demographic questions, 17 topic questions, and two questions for participants to provide additional comments and indicate their potential interest in participating in an interview or focus group to clarify their responses. The 6 demographic questions were all multiple-choice questions, with one question on scholarly discipline that included an open-text option. The 17 topic questions were designed around 7 aspects concerning the phenomenon of publication integrity that we identified based on previous literature and the team's knowledge of publication integrity, given their expertise. These categories are definitions and methods of assessing reliability (3 questions), research paper mills (1 question), PubPeer (1 question), experiences with unreliable publications (4 questions), reproducibility (3 questions), confidence in navigating the literature (1 question), and education on publication integrity (4 questions).

The topic questions were constructed in three formats. The first question type represented multiple-choice questions, where participants were asked to describe how they aligned with a statement. The second type of question was conditional open-text questions, where participants answered "yes," "no," or "prefer not to answer" and were then guided to a series of open-text questions that asked for brief responses, where responding was optional. The final category of questions consists of open-text questions, which include a text box for participants to type their responses. We limited the number of open-text questions and made responding to them optional to minimise survey fatigue (Braun et al., 2021). The complete list of survey questions is available in Supplementary File 1.

The survey was designed on Qualtrics XM, as this platform allowed questions to be accessible on any digital device (including phones), thereby increasing the likelihood of higher response rates (Toepoel, 2017). The survey began with an in-depth consent form and an information sheet that participants could download for their reference. The participant information sheet explained that the study was anonymous. Participants were only able to continue to the topic questions if they provided consent and addressed all demographic questions. For all other topic questions, participants could skip questions without responding, where a query box warned them about the lack of response. Although we advised completing the survey in one sitting, we used cookies to allow participants to pause and resume the study at any point, as participants were free to leave at any stage. Cookies also prevented multiple submissions. The anonymity of participants was ensured by turning off the recording of IP addresses and implementing standard encryption practices on Qualtrics, which ensures that any personal data is protected.

4.2.3 Piloting of the Survey

The survey was piloted with a small sample of 7 volunteers at the NSW Health State Biobank, who voluntarily identified themselves and consented to participate in the pilot. The survey was piloted from 02 February 2024 to 19 February 2024 for approximately two weeks. In this phase, the 7 participants were emailed a link to the survey and asked to complete it at their convenience. The pilot survey included open-text boxes where participants could provide comments on the survey design and we also emailed all pilot participants to report general feedback on the survey design. In the email, we inquired about accessibility, comfort with the questions, and the survey length. We

recorded the responses of pilot participants, as well as the time required to complete the survey, and the questions that were skipped. Generally, all participants expressed a favourable opinion of the survey, with some minor concerns about questions that might result in repetitive responses. We addressed these concerns in the final draft of the survey that was implemented (Supplementary File 1). Pilot responses were excluded from the survey results due to lack of anonymity.

4.2.4 Inclusion and Exclusion Criteria

We defined postgraduate students as any students undertaking a research training degree, such as a doctoral or master's degree. An ECR was defined as any researcher who completed their PhD or equivalent doctoral research degree within the past 10 years (2013-2023). We excluded participants who did not meet the above definitions or did not disclose their career stage. No restrictions were placed on participants' geographical location or their primary research or academic discipline. However, we restricted participation to researchers who could write responses in English to ensure clarity during analysis. To be considered to have made an active response, participants had to answer at least one open-text question. If a participant only answered closed questions and provided nonsensical responses to all open-text questions, they were excluded from further analysis. Data collection ended on 18 June 2024, and we included incomplete survey responses if they met the eligibility criteria described above.

4.2.5 Sampling and Recruitment

As this was a qualitative study, a convenience sample of participants recruited via social media with minimal restrictions was deemed appropriate. As no similar studies have been conducted, this study aimed to serve as an exploratory investigation, providing preliminary insights. Hence, we did not aim for data saturation or make any qualitative generalisations or statistical inferences, but to develop an understanding of the phenomenon.

The survey was primarily distributed in the form of a link or QR code, which linked participants to the Qualtrics form upon clicking/scanning. We did not offer any financial incentive for completing the survey. Participation in the survey was voluntary, and participants could exit the study at any time. However, due to the mechanisms used to ensure anonymity, withdrawing responses once written and submitted was not possible.

A multi-level recruitment approach, including communication via personal networks and partnering with eLife's ECR Ambassador program, which consists of a globally diverse network of researchers, was key to our sampling strategy. The team shared the survey link/flyer with the QR code on their own personal X and LinkedIn profiles. We chose these platforms because they were identified as commonly used by ECRs for academic and research communication (Le Busque and Mingoia, 2023; Jamali et al., 2020; Nicholas et al., 2017). Secondly, eLife also engaged with our own social media posts and posted their advertisements with the survey link on X and LinkedIn. Hence, by using a multi-level approach that combined our personal social media

accounts with eLife, we aimed to recruit a diverse group of participants. We promoted the survey for at least three months from 01 March 2024 to 18 June 2024, during which various team members and eLife made posts about the survey.

4.2.6 Data Collection

The survey closed at 11:59 p.m. on 18 June 2024, and all responses, both complete and incomplete, were recorded on Qualtrics. Responses to survey questions, participant progress across the survey (as a percentage of questions answered), time taken to complete the survey (in seconds), the date when the responses were recorded and whether the participant completed the survey were recorded automatically. Data were downloaded into Excel files and manually screened for eligible responses (Section 4.2.4), in consultation with the project supervisor (JAB). Data were manually reformatted to include responses from eligible participants. Any identifiable information was removed, and responses were corrected for grammatical and spelling errors. Each participant was assigned a numeric identity, ranging from P1 to P34. Upon de-identification, all Qualtrics files were deleted to ensure data security and confidentiality.

4.2.7 Data Analysis

Field notes were constructed from the de-identified Excel files for each participant. Each participant's response was then coded using NVivo software, guided by the field notes. Codes were analysed into themes according to Braun and Clarke's six-step data analysis process (Braun and Clarke, 2006) in an iterative process. Responses

were categorised into 7 aspects related to the phenomenon of publication integrity as designed in the survey (Section 4.2.2). Throughout this process, we wrote memos and created representative diagrams of the themes that were discussed at team meetings.

We placed the themes within a contextual framework, where we identified that ECRs and students navigated publication integrity as readers of publications, contributors and users of scientific knowledge, and in educational settings. For example, to understand how participants experience unreliable literature as contributors, we deconstructed the phenomenon into the experience itself, the response to the unreliable literature, and the perceived impact. When understanding how participants were impacted by engaging with unreliable publications, we generated codes from responses relevant to this aspect and analysed these into representative themes. We then linked each of these themes based on our interpretation into three mindsets: positive, neutral, and negative, which enabled the creation of a structured explanation of how participants experienced, responded to, and are impacted by unreliable publications. We then used this contextual framework to discuss how participants were affected by poor publication integrity, drawing on quotes that were deemed appropriate. As such, using empirical data and interpretive analysis, we created processes and frameworks that contextualised how ECR and postgraduate research student attitudes to, and experiences of, publication integrity across three contexts. In some cases, information was summarised in flowcharts constructed on MS PowerPoint or through word clouds generated using NVivo 15.1.0 to represent the diversity of opinions, accounting for stemmed words and using a minimum word length of 3. We also generated bar graphs in MS Excel, summarising information on responses to questions where participants were asked to respond on a Likert scale.

Response rates were calculated among the eligible participants on a question-by-question basis. We used the Mann-Whitney Test to compare median response rates between closed and open questions. A Spearman's Rank correlation was performed to examine the relationship between response rates and question position (indicated by number) within the survey. These findings were used to assess non-response biases within the analysed data quantitatively.

4.2.8 Data availability

We committed to ensuring participant anonymity and obtained consent for the survey on this basis. As such, although de-identified, the field notes and survey responses will not be publicly available, as there is no universal way to ensure participants cannot be identified through inference, particularly by colleagues or those who might be familiar with the participant. We have instead provided selected, de-identified quotes when explaining themes and understandings, ensuring that it is unlikely for participant identities to be inferred.

4.3 Results

4.3.1 Description of the two cohorts

Sixty-eight participants consented to participate, of which 44 (65%) actively responded to the survey, defined as the completion of at least one open text response. Ten respondents were excluded as they either did not disclose their career stage, had completed their doctoral degree more than 10 years ago, or had not provided at least one clear response (Figure 4.1). There were equal numbers of ECRs (n=17) and postgraduate research students (n=17) whose responses were deemed eligible (Figure 4.1, Table 4.1). Among the eligible student responses, one student was enrolled in a master's program, while the others reported undertaking a PhD or other equivalent doctoral qualification. The 17 eligible ECR respondents had completed their PhD 1-3 years (7/17), 4-7 years (5/17), or 8-10 years (5/17) prior to this study.

Among students, more participants identified themselves as female and were younger than the ECR cohort. Most ECRs and all students who listed a country/region that was part of the global north, particularly Australia (Table 4.1). The student cohort was also generally more research discipline diverse compared to the ECR cohort, where most participants listed 'Life Sciences and Biomedicine' as their primary research discipline (Table 4.1). Most respondents described previous experiences with unreliable literature and had some form of education in publication integrity, indicating a cohort with prior experience in publication integrity.

We also observed a statistically significant negative correlation between response rates and question position (ECRs: Spearman $R=-0.4808$, 95% CI=-0.7223 to -0.1349, $p=0.0072$, $n=17$; Students: Spearman $R=-0.4884$, 95% CI=-0.7270 to -0.1446, $p=0.0091$, $n=17$). Additionally, response rates to closed questions (with or without open text components) were significantly higher than those for open-text questions (Mann-Whitney $U=87.50$, median response rate for closed questions = 84%, $n=14$; median response rate for open questions = 62%, $n=16$, $p<0.0001$). This suggests that participants tended to respond more frequently to closed questions than open-text questions, and responses declined towards the end of the survey, indicating fatigue.

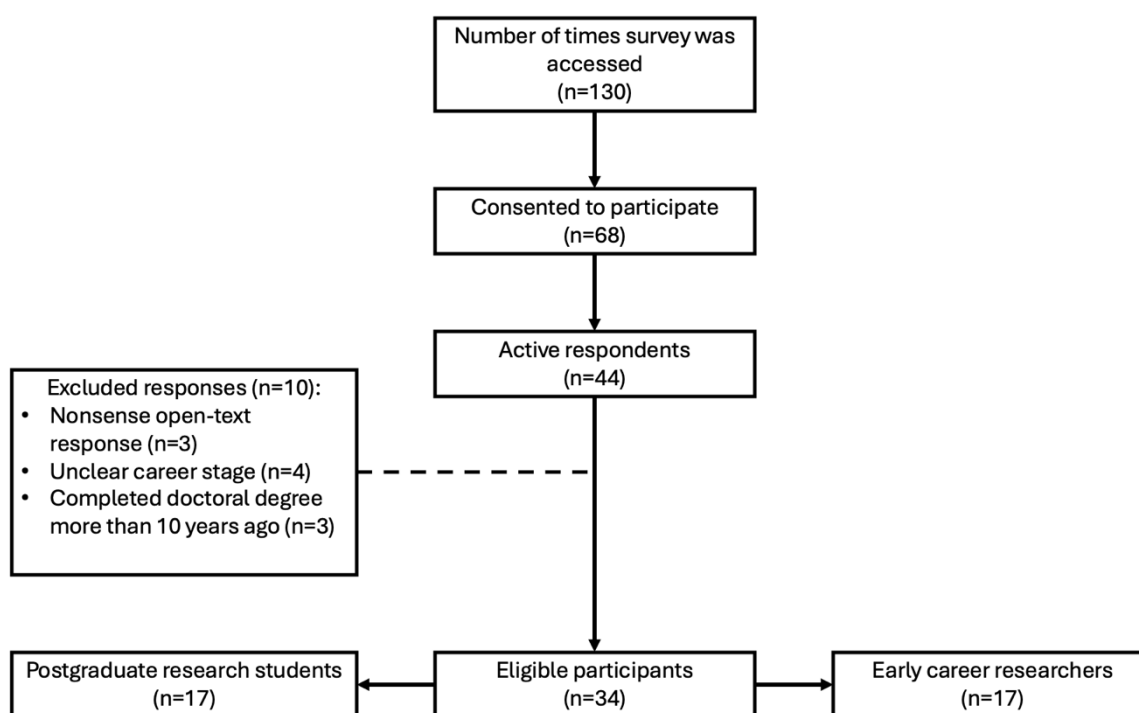


Figure 4.1. Overview of participant inclusion and exclusion, showing how respondents were filtered for in-depth qualitative analysis. Shown in brackets, all n-values indicate the number of respondents, except in the topmost box of the figure, where the n-value reflects the number of times the survey was accessed.

Table 4.1. Characteristics of eligible participants included for qualitative analysis

	ECRs	Postgraduate research students
Eligible Participants, n=	17	17
Gender		
Male	10/17 (59%)	4/17 (24%)
Female	6/17 (35%)	13/17 (76%)
Non-binary / third gender	1/17 (6%)	-
Age		
≤ 30	1/17 (6%)	11/17 (65%)
> 30	16/17 (94%)	6/17 (35%)
Location (by regions)		
Australia or NZ	4/17 (24%)	10/17 (59%)
Europe + UK	5/17 (29%)	6/17 (35%)
North America (USA, Canada)	4/17 (24%)	1/17 (6%)
Asia	2/17 (12%)	0/17 (0%)
Africa	2/17 (12%)	0/17 (0%)
English as first language?		
Yes	6/17 (35%)	9/17 (53%)
No	11/17 (65%)	8/17 (47%)
Primary research discipline		
Life sciences and biomedicine	13/17 (76%)	7/17 (41%)
Technology (including engineering, and information technology)	2/17 (12%)	0/17 (0%)
Physical sciences	1/17 (6%)	1/17 (6%)
Applied health	1/17 (6%)	2/17 (12%)
Social sciences	0/17 (0%)	6/17 (35%)
Statistics	0/17 (0%)	1/17 (6%)
Experienced unreliable research publications in their discipline?		
Yes	14/17 (82%)	13/17 (76%)
No	2/17 (12%)	3/17 (18%)
NR	1/17 (6%)	1/17 (6%)
Education on publication integrity?		
Yes	10/17 (59%)	9/17 (53%)
No	4/17 (24%)	4/17 (24%)
NR	3/17 (18%)	4/17 (24%)

NR = No Response

4.3.2 Definitions of ‘reliable research’

We drew on 31 participants (16 ECRs, 15 students) descriptions of reliability within their disciplines, where they were asked to describe how they define “reliable literature”. Two participants (one ECR and one student) disclosed that they were not sure of what constitutes reliability or whether the term reliability should be used. Otherwise, participant definitions of reliability collected around three main themes (Table 4.2, Figure 4.2). Most participants cited multiple ideas from the major themes and often discussed how reliability is a multifaceted concept.

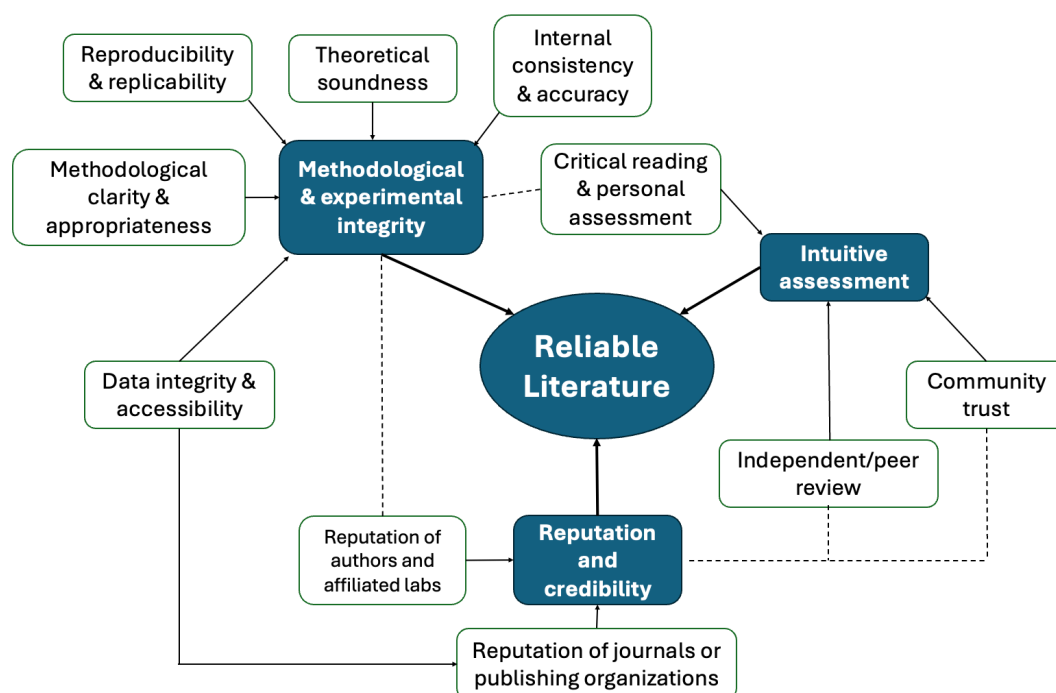


Figure 4.2. Relationships between themes uncovered from 29 participant responses when asked to define reliable literature. Participant responses were categorised into themes based on our background knowledge of publication integrity. Unshaded boxes represent codes that emerged from participant responses, which were organised (arrows) into three themes (shaded boxes) used to define reliable literature (centre). Dashed lines connect codes that can be mapped to multiple themes.

4.3.2.1 Methodological and experimental integrity

A dominant view that emerged from definitions of reliable literature was methodological and experimental integrity. Most participants cited clarity and detail in methods or results that can be independently reproduced (Table 4.2). Participants also noted the importance of using appropriate techniques and accurately interpreting the results (Table 4.2). Several participants also disclosed field-specific opinions of methodological rigour, such as the use of appropriate checklists, proper controls, and theoretical soundness (Table 4.2). Specifically, some participants also described the importance of well-conducted randomised control trials and systematic reviews with a high level of evidence assessed through quality assessment tools/checklists. Reliable literature must consider and accurately describe the limitations of the presented results, for example, “Literature that contains the proper controls, has used the right techniques to answer the questions and describes potential pitfalls of them.” (P28, Student).

Data integrity, accessibility and consistency were discussed as both foundations to ensure methodological and experimental integrity, as well as publishing standards by journals. Generally, participants described data integrity as having transparent sources that can be assessed independently, are theoretically sound, and have no signs of manipulation or unexplained inconsistency (Table 4.2). Participants also valued literature with methods that were transparently described, such that they can be reproduced independently (P25, Table 4.2). They also emphasised transparency in the context of replication and reproducibility, where they valued information that can be fact-checked and verified (P15, Table 4.2). Another ECR noted the importance of

data and code availability in ensuring replicability and thus the integrity of the data (P4, Table 4.2).

Another code within this theme was the consistency of the data within a study, such that there are limited contradictions, as described by a doctoral student: “The data globally all go in the same direction.” (P19, Student). According to one student (P2, Table 4.2), internal consistency was also framed in the context of replicability as another factor in determining reliability based on methodological and experimental rigour. Alternatively, as a student noted, poor data accessibility and integrity can be a product of publishing standards: “One of the reasons for doubting if the findings are accurate is because the authors might have done it with integrity, but the reporting of the study is limited to formatting from journals. Word limit and reviewers' comments to send it to the appendices compromise the reporting.” (P1, Student).

4.3.2.2 Reputations of authors, sources and journal practice

Another dominant view that emerged when defining reliable literature was to consider the reputation of the source in which the literature is published (Table 4.2). The most coded concept within this theme was the quality of journals, where several participants were noted to value high-quality journals, which could be broadly defined as journals with peer review practices, and a good reputation amongst their peers and the research community. Participants also recognised exceptions to relying on journals, finding literature from well-recognised organisations like the World Health Organisation, United Nations, and established standardisation bodies or organisations with high community trust to be reliable (P10, Table 4.2). Some participants were

sceptical of journals from certain publishers or those with lower IF, as one participant explicitly noted, “I do not trust MDPI papers” (P31, ECR).

Participants also describe the reputation of authors, both by their name and laboratories, as a factor when determining whether literature is reliable. For example, one doctoral student in statistics discussed recognition of authors: “...I will also consider the authors and affiliations - we are a small discipline and name recognition does help.” (P6, Student). One ECR noted that they are likely to find literature from “...laboratories known in the field for their rigour...” (P14, ECR). However, as indicated by another ECR, “Literature which comes from high-income countries is more reliable because they have all the resources and supplies to conduct high-quality studies.” (P13, ECR). This highlights a geographic and socio-economic bias, where affiliations from high-income countries are perceived to be reliable due to expected resource availability.

4.3.2.3 Intuitive assessments

Some participants described the importance of critical reading, where they assessed the reliability of each article according to their values (Table 4.2). For example, one ECR described how they relied on their intuitive perception and belief in the integrity of the publication (P29, Table 4.2). However, a doctoral student in social sciences formed their intuitive perceptions and judgements around replicability, “...research that I trust and that I think would replicate.” (P33, Student), indicating diverse opinions on what individual participants intuitively perceive as reliable literature.

Table 4.2. Summary of emerging themes from participants' definition of reliable literature

Theme	Supporting quotation
Theoretical soundness	"Reliable literature is that which presents a sound foundation - I want to see what the work has built upon and know that the foundation is solid. I want to see work that examines new methods from both a theoretical and empirical viewpoint. E.g., theoretical work supported by simulation." (P6, Student)
Methodological clarity and appropriateness	"Literature that makes clear reference to its sources, which can be readily found and assessed...Offers detailed description of methods and makes explicit the analyses used" (P15, Student) "In my applied work I want to see that appropriate checklists have been followed and reported on." (P6, Student)
Reproducibility and replicability	"Reliable would be something that has been reproduced or can be easily reproduced." (P19, Student) "...studies that are repeatable with consistent outcomes would be determined as reliable." (P2, Student)
Internal consistency and accuracy	"Reliable literature would regard appropriate methodological studies with correct interpretations..." (P2, Student) "[Literature] ...supported by clear figures with no signs of data manipulation, a detailed methods section to facilitate reproducibility and links to source data." (P25, ECR)
Data integrity and accessibility	"A reliable literature provides accurate, data-driven, unbiased, integrity-filled, specific information." (P20, ECR) "The evidence/results are clearly described (with materials including data and code) available and accurately replicates..." (P4, ECR)
Reputation of authors and laboratories	"Literature from known authors, from known journals with a good reputation. Authors from known labs." (P9, ECR)
Reputation of journals or publishing organizations	"Articles published in peer-reviewed journal or reports from the government/ well-known firms/organization (e.g., United nations, World Health Organisation...)." (P10, Student) "Any literature published in high quality journals." (P23, ECR)
Independent/peer review	"Reliable literature is literature...has been independently checked by a dispassionate and uninvolved party." (P7, Student) "...preferably has been peer-reviewed (or at least makes it clear that it wasn't)..." (P15, Student)
Community trust	"Literature published by an organization with high community trust...It also needs some sort of community buy-in like traditional peer review or whatever new models of community commentary that arise in the open science revolution." (P25, ECR)
Critical reading and personal assessment	"Reliable literature is literature for which I trust that experiments have been thoroughly and earnestly run at the best possible level with current methods, as well as analysed and presented in good faith." (P29, ECR)

4.3.3 Awareness of publication integrity as readers/consumers of the literature.

4.3.3.1 Methods of ascertaining the reliability of a peer-reviewed published finding

We analysed participant responses to understand how they judge a peer-reviewed published finding within their discipline as reliable. We asked participants to choose from 8 options: whether the publication was recommended by supervisors, a trusted research group or colleague(s), the IF of the journal where the article was published, whether it is highly cited, whether it aligns with existing literature, has a protocol, is pre-registered, (Figure 4.3) and we provided an open text box to report additional methods.

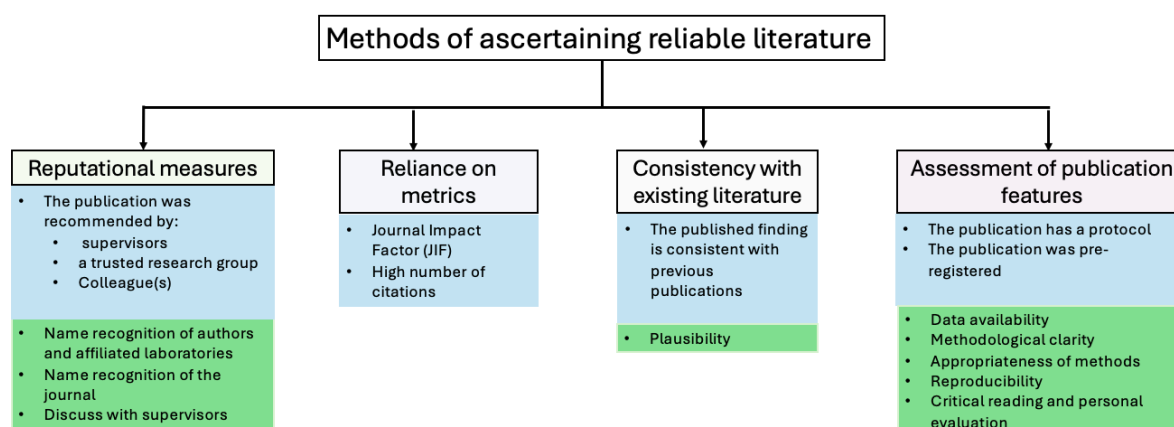


Figure 4.3. Summary of methods used to ascertain reliable literature categorised into four themes. Blue boxes represent methods selected by participants, green boxes outline additional measures reported by participants.

4.3.3.1.1 Assessing publication features and consistency with existing literature

Many participants emphasised assessing the integrity of publication by evaluating whether the paper adheres to well-established traditions, as well as features such as methodological integrity, transparency, data availability, reproducibility, plausibility, and internal validity/consistency of the study (Figure 4.3). Both ECRs and students selected the presence of a protocol and/or pre-registration as key signs used to determine if a peer-reviewed finding is reliable (Figure 4.3). Data availability was also noted to be a key indicator: “A combination of factors, but I place a high weight on the data and materials being available, protocol/registration made, clarity of the publication...” (P4, ECR). Assessments of integrity also included identifying whether the “Quality of the data shown in the paper is plausible and convincing.” (P14, ECR) and “...results of the publication can be replicated by others...” (P17, ECR). Participants also selected whether a publication is consistent with previous literature: “Other literature (previous or following) is not directly disproving the result.” (P15, Student).

4.3.3.1.2 Reputational measures and metrics

Another primary method of determining a publication’s reliability was reliance on reputation, either through the metrics associated with the paper or reputational measures of affiliations and authors. Several participants noted a reliance on metrics such as high citation counts and journal IF to determine whether a peer-reviewed finding is reliable (Figure 4.3). Notably, as reported by one ECR: “...checking it is not a predatory publisher or an unexpected venue for the quality of the work - i.e., I am suspicious of very low IF journals and quick turnaround times between submission and publication.” (P4, ECR). Numerous participants selected literature based on

recommendations from supervisors, trusted research groups or colleagues (Figure 4.3). Participants also noted name recognition of authors, their affiliated laboratories or the journal: “I know the authors/labs and I know they are good researchers.” (P9, ECR). Together, this represents a reliance on reputational measures guided by local networks.

4.3.3.2 How ECRs and students ascertain reliable publications

Most ECRs and students used various methods to assess literature reliability across the four major themes (Figures 4.3, 4.4). Few participants relied solely on methods focused on a single theme (Figure 4.4). Almost all students selected methods for determining reliability centred around assessing publication features (Figure 4.4A), such as “I can identify the analysis plan, the methods are sensible, and the data are available.” (P5, Student). Reputational measures were the second most common approach, followed by consistency with the existing literature, often used alongside methods of assessing publication features (Figure 4.4A). For instance, one student noted, “I read the paper and assess the internal validity of the paper or study by myself. If I have any queries, I ask my supervisor.” (P3, Student). Fewer students relied on metrics like citations or IF when evaluating literature, and most who did also assessed publication features (Figure 4.4A). One student (P21) only selected “the paper was highly cited” as a measure when evaluating the reliability of a published finding.

Conversely, most ECRs disclosed methods of ascertaining reliability that centred around the theme of reputational measures, where assessment of publication features was the second most selected, often in tandem with reputational measures (Figure

4.4B). Most ECRs who relied on metrics also showed used methods of assessing publication features and reputational measures when assessing reliability (Figure 4.4B). One ECR disclosed scepticism of low IF journals: “Checking it is not a predatory publisher or an unexpected venue for the quality of the work - i.e., I am suspicious of very low IF journals and quick turnaround times between submission and publication.” (P4, ECR). Whilst students’ perspectives on metric-based measures like IF were reported in the context of practices of integrity and critical reading, ECR perspectives were diverse and conflicting, where some relied solely on certain measures and others, similar to the student cohort, appraised the literature for reliability in a multifaceted manner.

4.3.3.3 How ECRs and students perceive the reliability of literature in their disciplines.

Most ECRs and students held a favourable view (agree-strongly agree) or neutral perspective on whether they “find the literature in my discipline to be generally reliable” (Figure 4.5). The two ECRs who solely relied on IF to evaluate the reliability of the literature (P12 and P27) expressed a favourable view, and in follow-up questions showed second-hand awareness of unreliable papers (Figure 4.4B). This suggests an implicit trust based on IF, and a possibly superficial engagement with the literature. A minority of respondents expressed pessimistic views about the reliability of publications in their discipline (Figure 4.5), stating opinions such as “Most published sh*t is wrong.” (P16, ECR) or “I frequently see research that does not pass a basic sniff test.” (P5, Student). Most ECRs and students who held pessimistic views also described assessing publication features when evaluating reliability (Figure 4.4A-B).

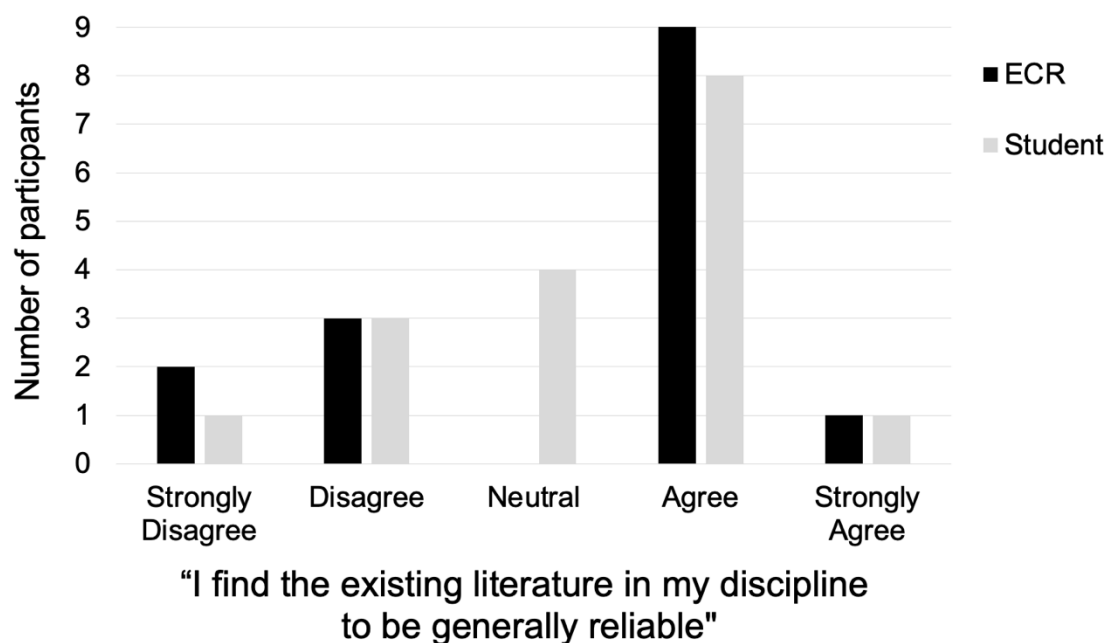


Figure 4.5. The number of participants (Y-axis) who responded to the question on their opinion of the reliability of the existing literature in their discipline, answered using the five-point Likert scale (X-axis). Responses from ECRs are shown in black, while postgraduate research students are shown in grey.

4.3.3.4 How confident are ECRs and students in their ability to identify unreliable literature

We asked participants to describe their agreement with the statement, “I am confident in my ability to identify unreliable publications in my discipline”. We drew from 27 participants (14 ECRs, 13 students) who responded to this question, where most (19/27, 70%) participants agreed, or strongly agreed, to the statement (Figure 4.6A). Participants who strongly agreed expressed high levels of self-confidence in their skills: “I am a good experimentalist and have a solid theoretical foundation.” (P32, ECR, Figure 4.6B).

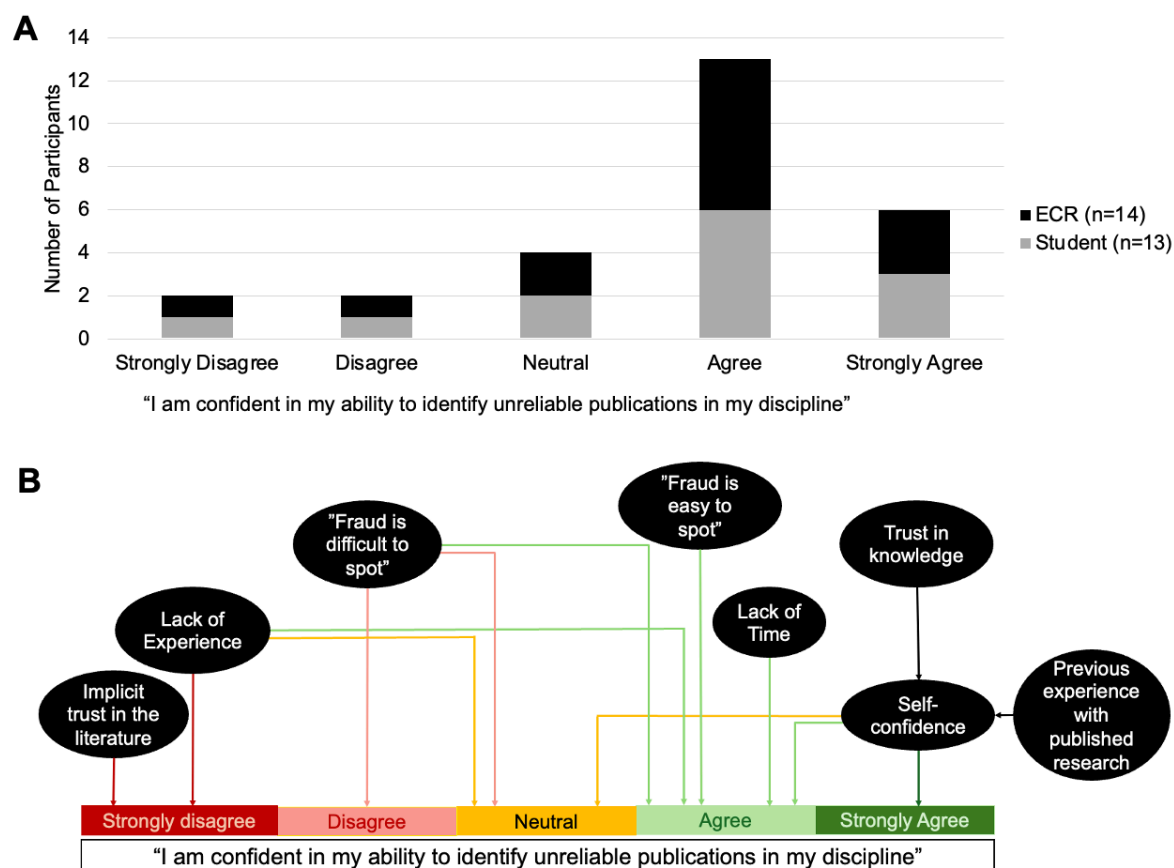


Figure 4.6. A) The number of participants (Y-axis) who responded to the question on to what extent they agree with “I am confident in my ability to identify unreliable publications in my discipline”, according to the Likert scale (Y-axis). Responses from ECRs are shown in black, while postgraduate research students are shown in grey. B) Schematic summarising the reasons why participants agreed or disagreed with the statement. Black circles outline reasons that are connected via downward arrows to participants’ responses (strongly disagree (dark red), disagree (red), neutral (yellow), agree (light green), strongly agree (dark green))

Among those who expressed lower levels of confidence, issues raised included concerns over “Time is the main factor - I think on average I am - but under tight deadlines it is much harder [to ascertain the reliability of papers].” (P4, ECR), and

perceptions around whether fraudulent research is easy or difficult to detect (Figure 4.6B). Some participants with weaker levels of confidence also expressed concern that there are “subtle issues that I am not yet experienced enough to identify” (P6, Student)

Some respondents disagreed or strongly disagreed with the statement (Figure 4.6A), expressing low confidence in their ability to detect unreliable papers. Such participants described that unreliable literature is “difficult to differentiate” (P27, ECR), or a lack of experience, “If you have not done similar experiments, it is hard to really know...” (P28, Student). The ECRs (P27 and P12) who expressed a lack of confidence also relied on metrics such as IF or citations to assess the reliability of published literature, along with an implicit trust that the research published in their discipline is generally reliable (Figure 4.4B).

4.3.3.5 How ECRs and students communicate suspicions about unreliable literature

We drew on 27 participant responses about with whom they would first discuss suspicions of a paper being unreliable. Most participants relied on their local networks, such as a colleague at their level or a more senior colleague. In contrast, few participants described consulting publishers or authors directly. Two doctoral students (P15, P24) also stated that they would consult no one and expressed confidence in their ability to detect unreliable papers. Within the open text responses, an emerging theme was that reactions depended on the reason why they engaged with the paper. For example, as P5 recalls, “It depends on what I need the paper for. If it is irrelevant,

nobody. If it is useful for my work, then first a colleague at my level, followed by a supervisor, then perhaps the journal if I suspect something.” (P5, Student). Alternatively, if the questioned paper was relevant to their work, ECRs and postgraduate students noted that they pursued their concerns, mostly by first reaching out to their local networks, and then to publishers or authors if their suspicions were confirmed. Very few participants described actively seeking advice beyond their local networks.

4.3.3.6 How do ECRs and students gain awareness of research paper mills

Thirty-one participants (16 ECRs, 15 students) responded to queries about whether they were aware of paper mills. Of this, 12 ECRs and 9 students described awareness of research paper mills. Amongst ECRs, most acknowledged the existence of paper mills within their disciplines. Some ECRs noted personal experience, such as suspicious citations, “There is no doubt from even the odd citations I receive on my papers.” (P4, ECR), or as another noted, “It is everywhere!” (P23, ECR). Others also noted firsthand experiences: “There is one big paper mill targeting my research discipline.” (P9, ECR). Other participants showed a general disregard for publications authored by paper mills: “...If you acknowledge that garbage [papers by paper mills]. Stupid people tend to do this. I am not stupid.” (P16, ECR). Most students expected that paper mills are active within their discipline: “I would be extremely surprised if they [paper mills] were not.” (P5, Student) or “...It would be naive to assume that they are not also active in the theoretical statistical fields, though I have not come across stories

of them.” (P6, Student), or “I bet they are! I work in consumer psychology.” (P15, Student).

Other participants were sceptical of paper mill activities within their research discipline. This sometimes reflected a lack of experience: “I would not have enough information to make an answer if they are or are not used in my research discipline.” (P2, Student), or “I do not know. I have basically only heard rumours.” (P25, ECR). Several participants demonstrated confidence in their disciplines, being resistant to paper mill activity. For example, one ECR noted, “My close community is based in Europe, and I know them personally. I believe I would have been aware if there was any.” (P31, ECR). Another ECR described how publications in their disciplines “...are associated with real-world settings, which would be challenging to recapitulate with paper mills.” (P27, ECR).

4.3.4 Experience of publication integrity as users of and contributors to the literature.

4.3.4.1 Experiences with unreliable publications

Overall, 32 participants responded to questions on whether they had experience with unreliable publications in their discipline. We drew upon 27 participants (14 ECRs and 13 students) who described their experience interacting with unreliable literature. We have summarised this as a process in Figure 4.7, depicting the major themes that emerged from participants' experiences.

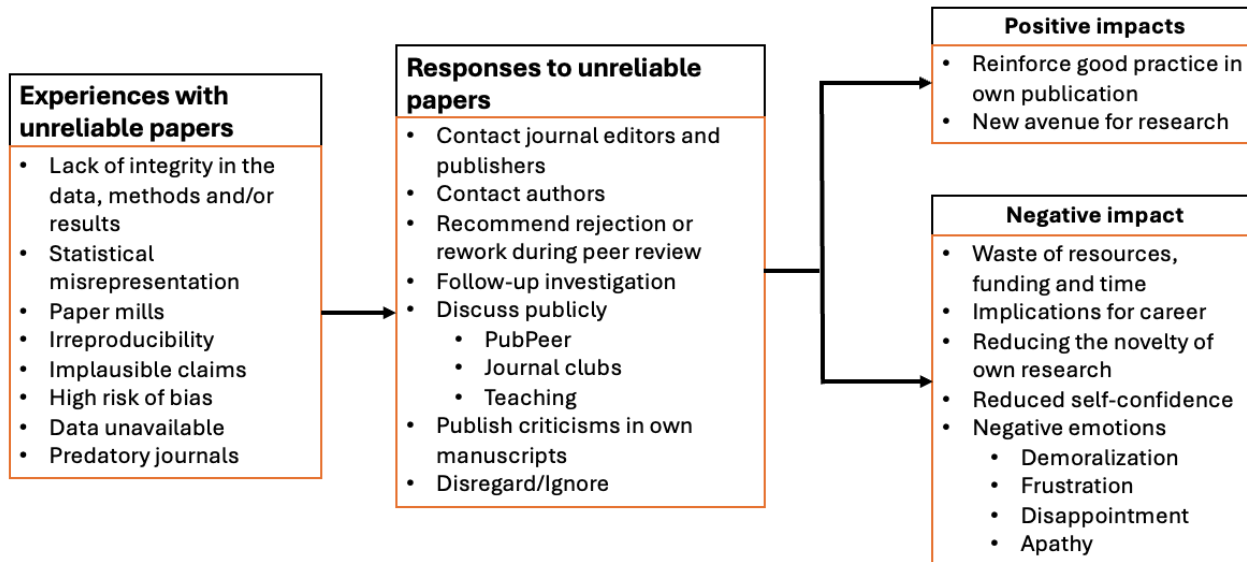


Figure 4.7. Flow chart summarising the major themes that emerged from participants' responses outlining experiences, responses and impacts of interacting with unreliable literature. Each dot point represents a theme that emerged from participant responses.

Most participants offered detailed accounts of their experiences in unreliable literature. Some participants could not recall specific details of unreliable literature, noting this as something “not memorable” (P34, ECR) or “Probably because you can spot them fairly easily in most cases and therefore do not become an issue in research.” (P30, Student). Amongst others, experiences with unreliable literature were diverse. One ECR noted: “There are plenty of examples I can say, which were retracted due to multiple reasons.” (P23, ECR). Several participants recalled retracted papers as a source of information or an example of unreliable literature: “I am a psychologist. I have read many problematic articles, such as Daryl Bem's publication and many of Diederik Stapel's papers (among others, less high-profile junk)...I knew they were not reliable; I cited them, and I actively discuss these types of papers as bad examples.” (P8, Student).

Many participants recalled having read published research that is not methodologically transparent and internally consistent. For example, one participant displayed a scepticism towards specific methods: “I tend to think that any publication involving machine learning is less reliable than publications that solely use mathematical models and physical experiments, as the fundamental methodology underlying these techniques seems to me, for now, to be on shakier ground.” (P4, ECR). Another participant stated, “Many studies are underpowered and have small sample sizes. Many times, I have found studies that, for whatever reason, disregard statistical assumptions in models that likely have results that are incorrect.” (P2, Student). Experiences of publications with statistical anomalies were also discussed in the context of data fabrication: “I read a paper that claimed Bayesian inference with informative priors amounted to data fabrication. One simulation study was provided,

but no proofs of any propositions were provided. It was published in an obscure Spanish journal outside of the statistics discipline.” (P11, Student).

Statistical anomalies were also discussed in the context of bias, “...The claims appear exaggerated, the data were contorted to fit a pre-specified conclusion, or perhaps the analysis appears scattergun, also known as clear evidence of fishing.” (P5, Student). Other participants discussed literature with a perceived risk of bias: “I have come across many publications with a high risk of bias, threatening the internal validity of the paper. For example, a case-control study not matching the two groups on certain confounding factors which could affect the outcome of interest, or randomised control trials not randomising the participants.” (P3, Student). Observations of bias were not limited to a particular discipline. One participant noted that papers with unreliable data/methodology led to the publication of results that “...contradict findings that are accepted as a general truth. I think it happened because of poor lab quality and lack of experience.” (P13, ECR). Participants discussed literature that was not transparent: “I find it rare to find publications where all data and code are available to reproduce.” (P4, ECR). Several participants also noted experiences such as “...protocols from publications that just never worked in my hands...” (P25, ECR).

Several ECRs described being aware of unreliable research through paper mill activity and predatory journals, for example, “I have found many paper-mill-generated papers. In my field, there is one very active paper mill author who publishes a lot of junk together with other authors. They have published a massive number of papers that most likely contain made-up data.” (P9, ECR). Participants also described predatory

journals: “It depends on the level of education, geographic location, funds and what is held as best practices in a locality. In the global South, predatory journals, which in most cases are not properly peer-reviewed, may not provide reliable data and scientific details, are abundantly available and unreliably used.” (P20, ECR).

4.3.4.2 How ECRs and students respond to and act upon unreliable published research

The primary response to unreliable literature was exclusion: “I often discount the findings and become more sceptical about the claims being made.” (P5, Student). Alternatively, several participants recalled including criticism in their manuscripts, “When I summarised the findings in my systematic review, I stated the field has problems with basics on reproducibility, clarity/scientific rigour, and therefore my findings were based on the field’s lack of quality - rather than trying to summarise findings from poor studies.” (P4, ECR). Other participants described discussing unreliable literature with colleagues or during teaching settings: “As I knew they were not reliable, I cited them and I actively discuss these types of papers as bad examples when I teach, give presentations on questionable research practices, or chat with colleagues.” (P8, Student).

Several participants also described efforts to correct the literature: “...one of us brought it up with an editor of the journal. The editor thanked him for pointing out the problems, but I do not believe it was ultimately corrected or retracted.” (P25, ECR). Participants also described reporting such concerns: “I warn publishers about these papers by sending them an (anonymous) message and I report it to PubPeer.” (P9,

ECR). Participants also described actions taken as peer reviewers: “I will typically recommend rejection or significant amounts of reanalysis.” (P5, Student). Participants described publishing a commentary: “I wrote a commentary on one of the clinical trial papers, where it has statistical analysis issues.” (P23, ECR) and “We tried to reproduce the findings and then published a debunking.” (P32, ECR).

4.3.4.2.1 Experiences with reproducing published findings

We also asked our participants whether they had attempted to reproduce a published finding. We drew on responses from 29 participants (15 ECRs and 14 students). In general, participants valued reproducibility as a core principle of science: “The purpose of science is to demonstrate a reproducible phenomenon. If I, as an educated academic, cannot reproduce a study’s results given the data and the code, the study is either poorly reported (at best) and questionably fraudulent (at worst).” (P5, Student). However, some students did not attempt to reproduce findings or failed in their attempts to do so, citing a lack of funding and resources: “I would be able to do it myself – seems very resource intensive.” (P15, Student). There was also emphasis on how original studies can be methodologically unclear or provide “...no access to manuscript raw data...” (P1, Student). In contrast, several ECRs noted that reproducing a published finding was not appropriate in their discipline: “In my particular area and research questions (computational modelling of evolution), I do not think it necessarily makes too much sense to try to reproduce published findings directly.” (P29, ECR).

Several participants also recalled attempting to reproduce the original paper and publishing the negative results: “A group from X Country published a not-even-wrong paper about a material they call X...[I] tried to reproduce the findings and then published a debunking.” (P32, ECR). In saying this, some also expressed doubts as to whether irreproducibility was due to circumstances: “I was trying to build on a finding from 2002, and unfortunately, it did not replicate. I was not sure if it was because things had changed in the past 10-20 years (it was a finding related to computer-mediated communication) or because the original finding was not robust or had been p-hacked.” (P33, Student).

Not all attempts to reproduce results were in response to unreliable publications, as some researchers attempted to reproduce findings due to interest in the protocol or methodology: “I once found a paper explaining a simple method. The researcher had used it to produce some nice results. Unfortunately, when I tried to implement that method, I never managed to see a significant difference between positive and negative control.” (P19, Student).

4.3.4.2.2 Perceptions of fault upon failing to reproduce a published finding

We offered the following statement: “If a finding is irreproducible, I am likely to believe that this represents a fault on my part rather than a problem with the published finding” (Figure 4.8). We drew on 28 participants (14 ECRs and 14 students) who responded to this question. Some gave nuanced responses (Figure 4.8): “There can be many causes for difficult replication.” (P29, ECR), and: “Depends. The fact that something is

irreproducible does not necessarily mean that either I am at fault, or the authors did something shady. There are nuances to this question.” (P8, Student).

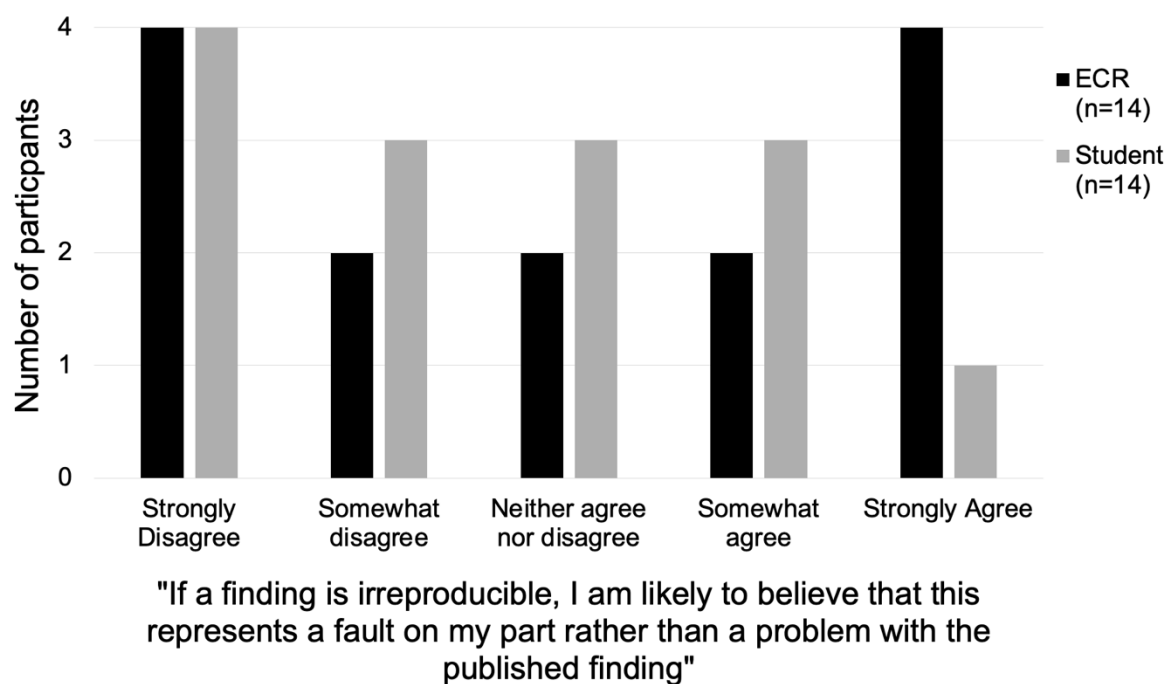


Figure 4.8. The number of participants (Y-axis) who responded to the question shown below the X-axis, answered using the five-point Likert scale (X-axis). Responses from ECRs are shown in black, while students are shown in grey.

Approximately half the participants suggested causes for irreproducibility lie within the original publication (Figure 4.8): “I often find the quality of work published is declining, so I strongly disagree - I am very cynical and sceptical when it comes to all research findings, including my own.” (P4, ECR) or: “When findings do not replicate, I do not think it's ever a "skill issue" on the part of the person trying to replicate. Published findings should have enough info that findings can be replicated using the same methods if someone wanted to.” (P33, Student). Several participants cited self-

confidence in their skills: “If I cannot make it work, the paper was bunk!” (P32, ECR). We also encountered participants who would suspect errors of their own: “Tend to assume that published results are correct and therefore it must be something I did wrong.” (P27, ECR) or “As much as I love research, I am not very good at bench work so I often assume I am messing something up rather than that the original authors were wrong unless I think it is wrong while reading the paper in which case I am unlikely to attempt the protocol.” (P25, ECR).

4.3.4.2.3 How ECRs and students view and utilise PubPeer

Thirty-one participants (15 ECRs and 15 students) responded whether they were aware of PubPeer, where 7 ECRs and 9 students agreed. Most participants defined PubPeer as an interface for post-publication review, with an emphasis on its capacity as a platform for discussing errors, limitations and the integrity of the published scholarly literature (Figure 4.9). Frequently mentioned terms in responses about PubPeer include ‘comment’, ‘discuss’, ‘publications’, and ‘review’ – reflecting that PubPeer is an online platform for post-publication review (Caron et al., 2024; Townsend, 2013). Another emerging view of PubPeer was its capacity to discuss errors: “You can discuss/highlight shaky literature there.” (P15, Student). Only one participant noted PubPeer’s plugin function: “...is a website (and browser plugin) allowing anonymous commenters to point out potential issues/limitations in published research.” (P5, Student). Another participant noted PubPeer as “...an online forum to discuss papers, give and get feedback.” (P8, Student).

Another group of ECRs and students were either unaware of PubPeer or described preconceived notions or limited knowledge about the platform. One student claimed not to know much about PubPeer, whilst another noted it as a “site for sharing and commenting on pre-published papers” (P6, Student), misunderstanding PubPeer as a pre-publication review platform. Other definitions of PubPeer also include the consideration of the platform as a community: “Online community, grass roots.” (P4, ECR).



Figure 4.9. Word cloud summarising responses of 7 ECRs’ and 9 students’ responses to ‘What do you know about PubPeer’. The word cloud was generated using NVivo

Several participants used the PubPeer platform to check publications for comments, whilst others described awareness of PubPeer and a lack of experience using the platform. Participants described using PubPeer to actively critique the existing literature: "I have contributed to PubPeer with at least XXX papers that I reported. Most were part of X paper mills." (P9, ECR). Another participant "...installed the plugin and searched for all of my publications (thankfully finding nothing)." (P5, Student). One student noted, "I actually only found out about it yesterday, but did enjoy reading critiques of a publication using some tortured and plagiarised language." (P7, Student). This perspective was shared by others who found PubPeer comments interesting and enjoyable to read: "I eat a lot of popcorn!" (P16, ECR).

4.3.4.3 Impacts of unreliable literature

Impacts in response to unreliable literature can be characterised as positive, negative or neutral, i.e. no impact (Figure 4.10). As discussed earlier, participants often described disregarding unreliable literature, and a group of participants believed that unreliable literature had no impact: “I have not experienced such impact.” (P29, ECR).

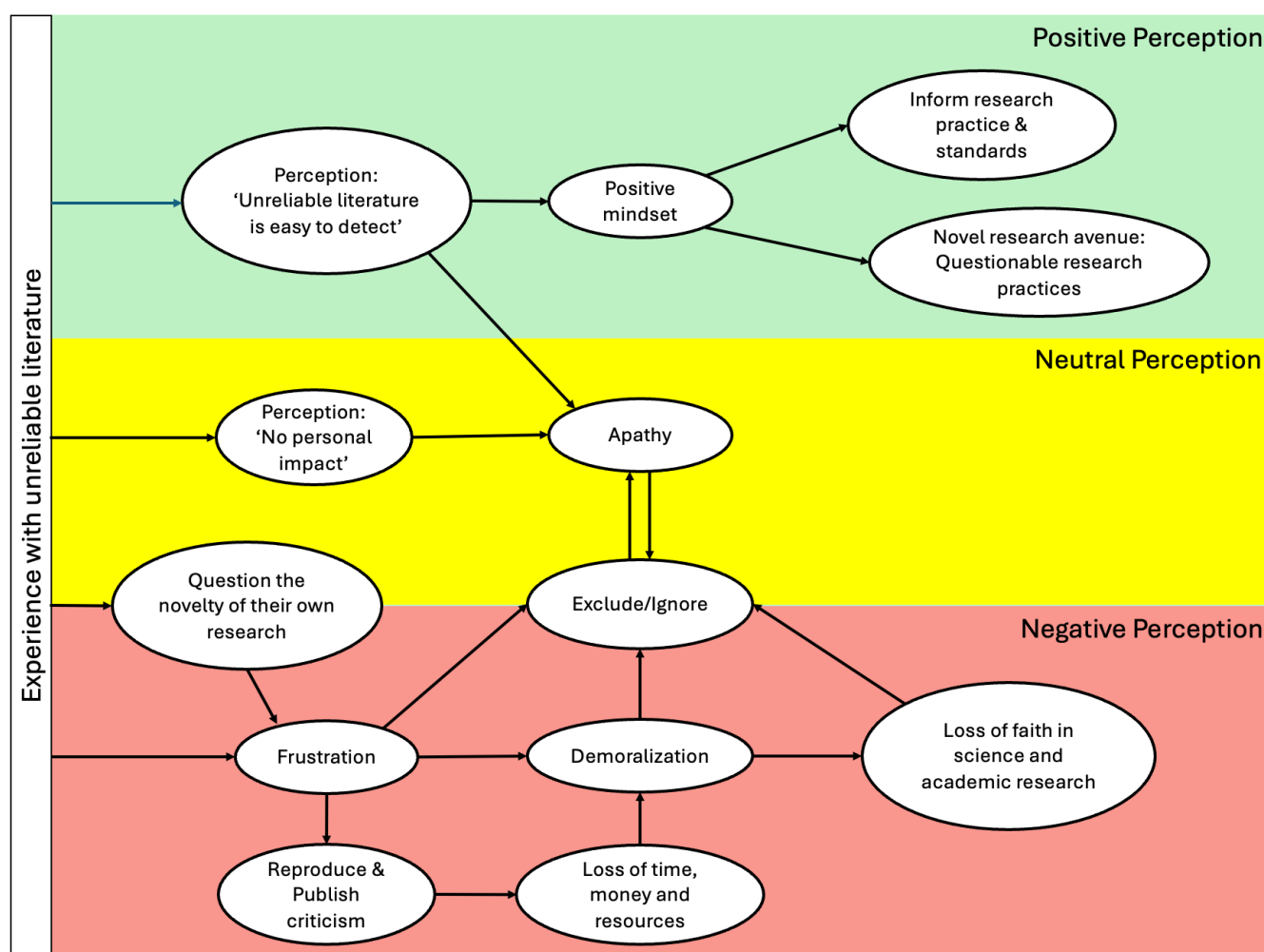


Figure 4.10. Participant perceptions regarding the impacts of unreliable literature and the interplay between reported impacts. The diagram is simplified for readability and does not reflect all impacts of unreliable literature described by ECRs and students.

Some students described positive impacts on their career and experience (Figure 4.10): “Within the master’s thesis, these [unreliable] studies were displayed tabularly with the assumed problems of the studies and justification. This formed part of the basis for the methodology of the study.” (P2, Student). Another participant described: “I chose to research questionable research practices because of unreliable papers and the sad state of science.” (P8, Student), reflecting that experiences of unreliable literature can generate novel research approaches. Others recalled that experiences with unreliable literature helped to form their understanding of best practices: “I make sure I do not repeat the same mistake I detected in others’ [unreliable] papers.” (P3, Student).

4.3.4.3.1 Negative impacts of unreliable literature

Many participants described feeling frustrated, depressed or annoyed at the presence of unreliable literature within their discipline (Figure 4.10). One student noted: “I am just disappointed. OK, sometimes I am mad too. I believe the replication crisis is getting worse, not better.” (P5, Student). Some participants expressed an apathetic view stemming from frustration: “By talking sh*t...this [interacting with unreliable literature] is life. Deal with it...Most published sh*t is wrong. Ignore it!” (P16, ECR). Such views were often supported by perceptions of detecting unreliable literature as an easy task: “You can spot them fairly easily in most cases and therefore do not become an issue in research...” (P30, Student), who later recalled that this is “...just annoying and frustrating to see.”.

Unreliable publications can cause issues during peer review: “I had to deal with unnecessary reviewer questions as a result [of unreliable literature].” (P32, ECR), which resulted in the participant needing to run a reproducibility study and then publish a commentary debunking the unreliable literature. They described this process as having a high material cost: “...it took a year and thousands in funding...” (P32, ECR). Consequently, some researchers expressed broadening scepticism: “...having more doubts about the research integrity of certain groups.” (P22, ECR).

Some participants also disclosed how unreliable literature had misled their research directions: “I wasted a lot of time in the first couple of years of my PhD trying to build on findings that ultimately did not replicate.” (P33, Student). Also, given how “negative results are not trusted” (P28, Student), some participants described that they might not be able to include findings about unreliable literature within their thesis. Several participants also expressed concerns about how others perceive their own work: “... [unreliable literature] impacts how likely other people consider my results.” (P28, Student).

Participants described publishing in predatory journals: “I unwittingly engaged with predatory journal publication, which provided unreliable publications that I cannot use in the later stage of my career.” (P20, ECR). Some participants also expressed concerns about correcting unreliable research they have published: “I worry that I have engaged in unreliable research due to errors made that I was unaware of as a student. I would be concerned about the implications of a journal article correction if I were to attempt to clarify some of those points. The bar is very high, and our current system

does not sufficiently allow for a study to be elaborated on or tweaked post-publication. It is a cultural issue that needs to change to address the inability to replicate many published papers.” (P5, Student).

Some participants shared detailed accounts of their experiences, expressing frustrations with research environments where publication counts are prioritised over quality: “Generally, it gets me down, I often think about whether this is the right career for me, as I do not often see people following good practice being credited (or surviving!) the systems we operate in. I now just see myself as a perpetual underdog, seeing how long I can survive operating the way I do with my own research practice (which is not usually rewarded for ECRs - slow and robust science is very high risk for staying in the system) ... do not think there's a day where I have not been cynical/frustrated! I now try to protect myself by focusing on my work being as reliable as possible, and that I am being the best researcher I can be, as I cannot control the behaviour of others, and often you cannot report where they are behaving badly due to their power positions.” (P4, ECR). Such experiences led to participants questioning their career directions: “It makes me question the point of staying in science.” (P9, ECR).

4.3.5 How ECRs and Students learn about publication integrity

Most participants (10 ECRs, 9 students) described receiving formal education on publication integrity. Some expressed the view that “Publication integrity is vital to outcomes. Without integrity, it would be possible that incorrect, harmful or possibly dangerous studies may be considered accurate.” (P2, Student), and that training has enabled them to personally “...make sure I was starting a research career with all the required info to make correct choices.” (P6, Student). Some participants recalled learning about publication integrity through “courses, lectures, workshops” (P3, Student) available within their institutions. Several participants, particularly students, stated that institutional training was mandatory, often “when starting my PhD” (P6, Student) or that they had a “curriculum or funding requirement” (P25, ECR). Amongst participants who received formal training, some described institutional training as contractual, with an emphasis on “...plagiarism and copyright, but much less about publication integrity beyond licences.” (P15, Student).

Four ECRs and five students described receiving no formal education on publication integrity. These participants described the view that publication integrity is “...solely the domain of people interested in meta-research.” (P5, Student) and hence explained that within their discipline, publication integrity “is not really taught” (P5, Student). A more common perception was that mandatory training involved “worthless non-binding classes” (P16, ECR). This was described at length by another participant:

“There are so many mandatory courses via institutions, but rarely (if ever) does that translate. I see examples of senior leaders (DVCR/PVCRs) who have breached

XXXXX's responsible conduct regarding their involvement in publications. That is where I become incredibly cynical, and ECRs are in a very vulnerable place to report this - often we are advised privately to just get the project over with ourselves, even if the author has not contributed, and 'move on'. There needs to be far more accountability for those in leadership and senior positions where junior researchers can report breaches without it leading to career suicide." (P4, ECR)

4.3.5.1 Learning about publication integrity through external sources

Participants recalled learning about publication integrity through local mentoring networks or seeking information sources external to institutional programs, for example: "from professors in the field" (P1, Student), and: "Simply being explained how to check that your data is reliable to make sure you are not spreading false information." (P19, Student). Some participants also educated themselves through firsthand experience, where they "...dig a bit deeper...became more aware of it all and started to actually focus on it and actively look for fraud/unethical issues with papers." (P9, ECR).

Education in publication integrity outside institutional programmes was motivated by a general interest in the integrity discourse as a foundational principle of science, "it [publication integrity] is necessary if we want science to progress." (P19, Student). Some participants also expressed concerns, "Gut feeling the system is off!" (P1, Student). As such, education in publication integrity was perceived as a necessity in countering the increasing numbers of unreliable literature; "It [education in publication integrity] is necessary if we want science to progress." (P19, Student).

4.3.5.2 How ECRs and students learn about PubPeer

Local networks played a key role in how participants learned about PubPeer, where many noted how they were introduced to the platform by peers or more senior colleagues. For example, one participant noted how they learned about PubPeer “...through a senior statistician in my organisation.” (P7, Student). Others described learning about PubPeer through Twitter/X, and academic presentations where one ECR noted “I have heard about it countless times, including a presentation by one of its founders.” (P29, ECR) or through news on sites like ‘Retraction Watch’. Students also noted that they learned about PubPeer through their “work in the publishing industry” (P15, Student) or their research into questionable research practices. No participant explicitly mentioned learning about PubPeer through formal education programs.

4.3.5.3 How ECRs and students learn about paper mills

Thirteen ECRs and 9 students who were aware of paper mills disclosed how they learned about such organisations, and their perceptions of paper mill activity within their disciplines. Most participants recalled becoming aware of paper mills through online posts on social media such as Twitter/X, or platforms such as “ForbetterScience.com” (P32, ECR) or Retraction Watch (P6, Student). For example, “I have heard about it on Twitter, and in newspaper articles focused on issues in the scientific publication system.” (P29, ECR).

Some participants described Metascience or AIMOS (Association for Interdisciplinary Meta-Research and Open Science) conferences as places where they had been made

aware of and/or learned more about paper mills. One participant described learning about paper mills through "...the 'Everything Hertz' podcast by James Heathers and Dan Quintana. I learnt a lot through them - and then became very engaged and started attending AIMOS conferences..." (P4, ECR). Several participants described learning about paper mills through working in the publishing industry. One participant recalled academic talks that they had attended: "I gained awareness of paper mills when listening to lectures and talks on research integrity. It was unknown to me before looking into research integrity." (P2, Student). No participants mentioned their institution's research integrity courses or programs as a source of awareness about paper mills

Some participants recalled how they had encountered publications that appeared to be from paper mills: "I noticed a particular author to publish an insane high number of papers, when checking some, I started to notice errors...this author publishes in several different fields, which makes no sense." (P9, ECR). Another participant mentioned that: "I know someone who worked in a salami slicing factory." (P5, Student).

4.3.5.4 How ECRs and students learn about reproducing published literature

Predominantly, we identified two paradigms through which participants learned to reproduce published findings. Firstly, several participants described that the skills required to reproduce a published finding are "...the same ones that are required to obtain the findings in the first place" (P29, ECR). The second paradigm considers

reproducibility as a skill that requires training. Participants recalled the importance of first-hand experiences of working on research reproducibility projects, with numerous participants citing experiences in “psychology and cancer reproducibility projects” (P15, Student) or “training from research teams” (P24, Student). In the context of institutional coursework, very few participants recalled either learning about reproducibility during “university units of studies” (P24, Student). Many cited sources of learning that were external to doctoral programs, including “reproducibility networks webinars” (P23, ECR) or participating in “XXXXXXXXXX workshops and online webinars” (P2, Student).

Most participants perceived that learning first-hand was the best way to learn about reproducibility: “Doing something first-hand is one of the best ways of learning, in my opinion.” (P33, Student). Amongst participants who held reservations on the effectiveness of these methods, concerns included a lack of clarity on “...whether problems are on my end or the literature's end.” (P25, ECR) and assumptions of trust where “Nobody fakes results on purpose.” (P32, ECR).

4.3.5.5 Need for further education in publication integrity

Most ECRs and research students highlighted a need for further education in publication integrity, with an emphasis on “The limits of what is acceptable - where to report some [unreliable] works.” (P31, ECR). Participants described how “providing examples is the best way to learn” (P24, Student). Some participants were interested in learning about “How prevalent these issues are collectively, and if different fields are affected disproportionately by some areas than others.” (P2, Student). Another

participant expressed interest in learning about “The reasons that cause people to write papers that are (thought to be) unreliable.” (P29, ECR).

When asked whether participants would like to receive further education in publication integrity, two ECRs and two students stated that they do not need further training. Such participants described themselves as “well aware and up to date” (P9, ECR) but rather “...like to keep an eye on that kind of thing as and when it crops up (e.g., the Francesca Gino stuff).” (P5, Student).

4.3.5.5.1 Preferred form of education in publication integrity

When asked about the mode in which they would like to receive education on publication integrity, there were mixed opinions (Figure 4.11). Some preferred: “Online access makes it very easy and quick.” (P2, Students). In contrast, in-person learning was perceived as “most efficient” (P27, ECR) as “dialogue is important for this kind of learning” (P25, ECR). Didactic forms of education were centred around instructions such as reading material, where reasons for such preferences included “convenience and ease of engagement” (P15, Student) and that “Reading material is a useful resource to refer to as needed.” (P6, Student). However, such forms of education were perceived by some as boring: “I would not have the patience to sit through a lecture, it is kind of a dry topic when delivered didactically.” (P5, Student). Interactive education with active discussion was valued: “...do not believe that standards are always black/white, need to discuss.” (P31, ECR). Some preferred learning methods were lectures that included both didactic and interactive elements (Figure 4.11), “Lectures

are good, particularly if there is discussion between presenters and audience.” (P6, Student).

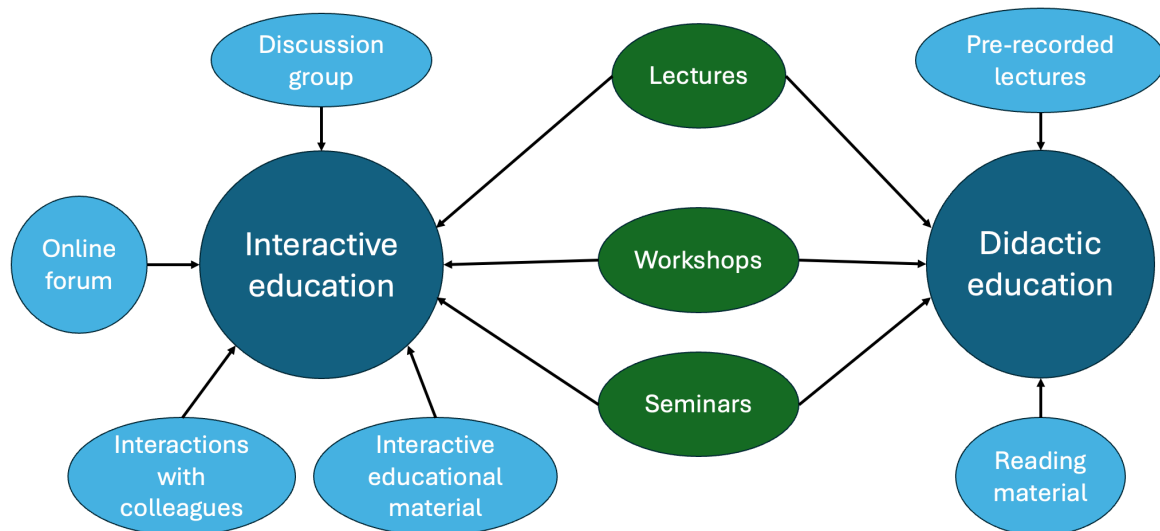


Figure 4.11. Summary of preferences in learning methods for education in publication integrity. Each circle represents a theme, with the large dark blue circles indicating the two main modes: interactive and didactic. Small light blue circles denote specific learning methods, while green circles represent modes that combine interactive and didactic elements. Arrows link methods to their respective modes of learning.

4.4 Discussion

4.4.1 Principal findings – describing publication integrity

Publication integrity is a multi-factorial construct that ECRs and students experience in three contexts: (i) as readers/consumers of the literature, (ii) as active contributors to/users of the literature and (iii) in educational settings. As consumers of the literature, we observed a diverse array of opinions about what constitutes reliable research and how participants ascertained reliability. Students' methods of ascertaining reliability predominantly used measures associated with assessment of publication features, whereas ECRs focused on reputational indicators such as name recognition of the authors, affiliations and journals or whether trusted individuals within their local networks recommended the paper. We also observed opinions from participants with minimal understanding of publication integrity to those with expert knowledge. Participants who lacked expert knowledge tended to rely on metrics or reputational measures. Some participants were experts who had directly contributed to the literature through their research on questionable research practices and showed in-depth awareness of problems such as research paper mills.

ECRs and students were also contributors to and users of scientific knowledge, building upon existing research publications and responding to unreliable ones. Their experiences included recognising retracted papers, analysing methodological inconsistencies, and being aware of issues such as irreproducibility within their discipline. The consensus response amongst participants who were cognisant of unreliable research was to exclude and disregard such publications. Some participants

publicly disseminated concerns through teaching, commenting on platforms such as PubPeer or pursuing post-publication editorial notices. A key element of these responses was that participants disregarded unreliable literature due to their awareness of its unreliability and hence were capable of actively excluding or critically discussing unreliable papers in their fields. In the absence of such awareness, researchers and, particularly, students seem more likely to use unreliable literature to inform their research or to waste time and resources pursuing irreproducible and unreliable research.

We can categorise participants into two mindsets based on their contributions to publication integrity. In the first relatively positive mindset, ECRs and students actively contributed to research on publication integrity, defining it as a discipline where some described studying paper mill activity or questionable research practices or through their capacity as peer reviewers. These researchers were confident in their ability to detect unreliable papers and/or that any irreproducible results they encountered were due to problems affecting the original paper. They discussed championing publication integrity within their local contexts or at least ensuring that their work is published with integrity. A second, more negative mindset emerged from frustration, anger and disappointment at the systemic and personal problems they faced due to poor publication integrity. Several participants recalled attempts to correct unreliable literature but faced a lack of response from publishers. Others noted difficulties during peer review, due to unreliable findings challenging the veracity and novelty of their own findings.

We also observed ECRs and students who doubted their skills to evaluate the literature, or when encountering irreproducibility, stated that they were likely to believe that the fault lay with themselves. Furthermore, as one participant recalled, systemic and cultural biases are created where advanced career progression can be achieved by those who publish papers of poor integrity, and due to the difficulty in questioning existing research, both formally through publications and informally with senior figures. Such experiences can combine and amplify feelings of apathy, frustration and disappointment, creating demoralised attitudes that can make junior researchers question the value of staying in academia.

Participants also described interacting with publication integrity in an educational setting. Education in publication integrity was widely regarded as essential and foundational. This was especially noted by participants who had experienced unreliable literature first-hand or who described unsatisfactory levels of education, particularly institutionally mandated programs that were perceived as ineffective or not translatable. Others who learned about publication integrity through experience and felt they had received satisfactory education to the extent that they felt that further training was unnecessary. Hence, a predominant view was that much of the practical education in publication integrity is driven by self-interest and individual curiosity, as opposed to institutionally provided training. Amongst the participants who viewed such education to be unnecessary, an emerging view was that reproducing findings or evaluating the literature capitalises on existing skills as opposed to requiring additional training.

Topics that participants expressed an interest to learn further about included publishing standards, including examples of reliable vs unreliable papers, how to report unreliable publications, the prevalence and extent of unreliable publications within and across disciplines, and motivations for why people published unreliable papers. In terms of preferences for modes of education, a conflict arose between effectiveness and convenience. Interactive, in-person forms of education were preferred due to their ability to invoke discourse, whereas traditional didactic forms of education were preferred based on convenience and access.

4.4.2 Strengths and Limitations of this study

Before we interpret the key findings further, we must recognise the strengths and limitations of the present study. The strength of our study lies in the rich detail of the perspectives and accounts presented by ECRs and research students from a range of disciplines, ages and countries (Table 4.1), at a time when research integrity and trust in science are topical. In the past few years, scientific integrity has increasingly been questioned by both the public (Boetto et al., 2021; Lynch et al., 2025) and by the researchers (Byrne and Barnett, 2024; Parker et al., 2024; Schmidt, 2021). Furthermore, an exponential rise in retractions (Chen et al., 2018; Gaudino et al., 2021), particularly by high-profile authors (Gross, 2016), has brought publication integrity into mainstream discourse, where many have begun questioning the integrity of the scientific enterprise. This suggests that researchers are likely to have encountered publication integrity issues in various contexts. Simultaneously, there have been numerous attempts by government organisations (Wang et al., 2025), publishers (COPE & STM, 2024; Else, 2022) and researchers or institutions (Abdi et

al., 2021b) to implement solutions that will improve research integrity and trust, with an emphasis on fostering integrity through training ECRs and students (Nicholas et al., 2019). However, no previous study has examined how ECRs and researchers understand and engage with publication integrity, and as such, our study addresses this crucial gap in knowledge.

In saying this, our study is not without limitations. Firstly, our study employed a convenience sampling methodology, where we leveraged social media profiles for recruitment. As our author team has published work assessing the publication integrity of their respective discipline (Byrne and Barnett, 2024; Pathmendra et al., 2024; Schmidt, 2021), our networks may consist of ECRs and research students who are generally more receptive and interested in publication integrity than most researchers. Additionally, most survey participants, particularly students, were from affluent countries (Table 4.1), which could be a product of various factors such as restricting the survey language to English, and to recruitment methods being potentially biased towards local networks. To attempt to overcome these potential biases, we cooperated with eLife's ECR Ambassador program (eLife, 2025), which is a globally diverse community (eLife, 2024). This cooperation could have resulted in ECRs from countries in the global south, particularly in our study. In an ideal situation, we would have liked more representation from the global south, yet available resources may have limited participants.

Participants with minimal engagement with publication integrity were less likely to provide in-depth responses. As such, detailed responses were likely to come from

students and ECRs who were already engaged with publication integrity. We also recognise that our decision to use an online survey was driven by convenience, access and resource availability. We observed a decline in response rate between earlier and later survey questions, with more thorough responses to earlier questions about publication reliability compared to questions about education at the end of the survey. This suggests that most participants experienced some form of fatigue due to the high number of questions.

Whilst an advantage of anonymous surveys is the assurance of confidentiality, which allows participants to candidly disclose their opinions (Murdoch et al., 2014), we must recognise that interviews and focus groups can provide more in-depth data in understanding phenomena (Mortari et al., 2023). However, the lack of previous literature on this topic also meant that we lacked the context and frameworks required to develop interviews or focus groups. As such, the present study is an exploratory step in understanding publication integrity, which more in-depth focus groups, interviews, and quantitative studies can then follow up.

4.4.3 What this study adds to the existing previous literature

Our findings indicate that publication integrity is multifaceted, where ECRs and postgraduate research students can play key roles. As such, there is a need to extend the definition of publication integrity as solely concerned with the quality or trustworthiness of the literature (Bolland et al., 2025; Rifai et al., 2019; Schmidt, 2021).

4.4.3.1 Publication integrity – as readers of the literature

Echoing a common view held when interpreting research integrity (Armond et al., 2024), there is an apparent lack of consensus on what constitutes publication integrity, as this is contingent on one's own experiences and values. It has been recognised that amongst postgraduate research students, there is a reliance on summarising the existing literature as opposed to critical analysis when writing reviews (Shahsavari and Kourepaz, 2020). Echoing this, we found a group of ECRs and students who described holding an implicit trust in the literature and who relied on metrics such as IF and citation numbers to guide their reading as opposed to critically engaging with papers. We also identified a group of ECRs and students who were more sceptical of the literature and employed critical reading, assessing whether the data were consistent or the methods were accurately reported. Where ECRs tended to adopt reputational measures such as recommendations from supervisors, students mainly described assessing publication features. We acknowledge that this could be partly due to sampling bias, but it may also reflect differences in how ECRs and postgraduate students engage with the literature.

4.4.3.2 Publication integrity – as users and stewards of scientific knowledge

As contributors to scientific knowledge, researchers have a responsibility to uphold publication integrity, as well as use the literature to build on the existing scientific knowledge through their contributions. Echoing the experiences of senior researchers and principal investigators (Schmidt, 2021), ECRs and students reported a variety of experiences through unreliable publications, ranging from irreproducibility to

suspected paper mill activity and predatory publishing. However, many ECRs and students stated that they ignored problematic papers, choosing not to pursue further action, as they recognised their lack of power and concerns over possible repercussions of voicing their concerns (Horbach et al. 2020; Pupovac et al. 2019).

Participants also described career incentives that are not aligned with the practices of integrity and the current publishing system. The primary route to act on unreliable publications is to seek editorial responses (Townsend, 2013). However, such processes are remarkably inefficient (Parker et al., 2022) and can be very slow (Byrne et al. 2021, Ortega, 2021). ECRs and students described how they work under time and resource constraints, where the cost of seeking action on unreliable publications can be damaging. Furthermore, ECRs described growing frustrated and eventually demoralised, echoing the general dissatisfaction with academia driven by the hypercompetitive environments and 'publish or perish' (Christian et al. 2021). Feelings of frustration were also attributed to a decline in self-perception as good researchers, driven by a lack of confidence in their skills. This was also echoed by Lubega et al. (2023), where experiences of irreproducibility by biomedical doctoral students were associated with intense feelings of self-doubt, frustration and depression that were strong enough to impact daily functionality and ability to work.

As noted by Schmidt (2021), principal investigators expressed frustration about unreliable papers that reduced the novelty of their findings or impacted peer review processes. Some ECRs and students also echoed these concerns, describing how unreliable papers were used to question the validity of their publications. However, not

all experiences were negative. We encountered ECRs and research students who had transformed such experiences into positive outcomes, where interactions with unreliable literature resulted in novel research avenues or reinforced their understanding of best practices. Several participants also attempted to leverage their roles as peer reviewers or within local networks to champion publication integrity, reflecting the passion and interest in integrity held by some within this demographic.

To the best of our knowledge, this is also the first study to investigate ECR and student awareness and understanding of research paper mills and PubPeer. Whilst many amongst the sleuthing community perceive research paper mills as a serious threat to the foundations of science (Parker et al. 2024; Parker et al. 2022), it is evident that there are groups of ECRs and students who remain unaware of paper mills. This lack of awareness about concerns and threats to publication integrity shows that researchers who work in publication integrity might be operating in an echo chamber. Our understanding and experiences may differ significantly from those of researchers who do not actively engage with publication integrity.

We also encountered some ECRs and students who either misunderstood the function of PubPeer or were unaware of the platform entirely. This suggests that some research community members are unfamiliar with PubPeer and its functions, and are not utilising it to its full potential, despite contrasting opinions that PubPeer has generated a significant additional workload for institutions (Caron et al. 2024).

4.4.3.3 Publication integrity – in educational settings

Within educational settings, most participants expressed that existing, often mandatory educational programs are ineffective or do not address publication integrity in a meaningful way. This was echoed in the context of research integrity training (Haven et al. 2019a), highlighting the need for more comprehensive education and mentorship. In contrast, ECRs and students who recalled satisfactory education described sources of information external to institutional programs that they often pursued due to self-interest or encountered by chance. Opportunities included participation in reproducibility projects (Fraser et al. 2023), actively questioning literature within journal clubs or projects guided by supervisors. This highlights how mentoring is important in fostering publication integrity, as opposed to standardised coursework that was often perceived as ineffective.

We also found that ECRs and research students preferred different styles and modes of education based on either convenience or practical effectiveness. Several participants stated that publication integrity cannot be taught didactically (despite this being perceived as more convenient) and instead requires discourse through discussion groups or online forums. In academic integrity (Jagiello-Rusilowski, 2017) and research integrity (Koterwas et al., 2021), such dialogue-based, interactive forms of education have been perceived to be more effective due to the development of discourse between participants and the real-world relevance of skills taught. We also observed a tension between convenience and effectiveness when it came to whether participants preferred online or in-person modes of teaching. While in-person learning is perceived as more effective, online modes remain convenient (Photopoulos et al.

2023). They are well-suited to the busy schedules of ECRs and research students, reflecting the need for hybrid forms of education in publication integrity.

4.4.4 Recommendations and further research

As an exploratory study, we recognise that we have not captured a complete description of how ECRs and research students navigate publication integrity due to the under-representation from the global south, who particularly lack research integrity infrastructure (Bain et al. 2022), or how hypercompetitive research environments could incentivise practices that lead to poor publication integrity (Zhang, 2025). Nevertheless, the information that we have obtained can serve as a basis for more in-depth focus groups and interviews. Future studies can expand and deconstruct the intersectionality of the three publication integrity contexts as consumers, contributors/users, and the recipients of education. Future studies will also benefit from analysing a large sample size across different career stages, such as students who have started their candidature, those who are finishing, early career researchers who have just completed a PhD, as well as those in later years. Due to the timing and length of our survey, we did not ask how the use of artificial intelligence (AI) affects publication integrity. Going forward, research will be necessary to understand whether AI use could affect how ECRs and students navigate publication integrity.

Replicating shorter versions of the current survey (such as the focus on paper mills or experiences with unreliable research) across institutions or at a national level could help to characterise the prevalence of ECRs and postgraduate research students who are affected by specific issues or lack sufficient education. Furthermore, due to the

voluntary nature of survey participation and recruitment strategy, we may not have captured former ECRs and students who have since left academia. Given that we identified several participants who expressed demoralised attitudes to the point of questioning their career paths, it is likely that students and ECRs have left academia due to the repercussions of engaging with unreliable publications. Investigating this group's experiences will be crucial in further understanding the extent of harm caused to ECRs and students by poor publication integrity.

Our results also highlight the importance of prompt post-publication corrections, not only as a safeguard against research waste and harm, but also to demonstrate that publishing unreliable research has consequences. Although alternative systems like PubPeer have been developed for post-publication commentary (Caron et al., 2024; Townsend, 2013), not all ECRs and students are aware of them. Therefore, we should increase exposure to PubPeer through educational programs. We can also advocate re-establishing PubMed Commons (Byrne and Barnett, 2024; Dolgin, 2018), a former post-publication platform connected to the PubMed that many ECRs and students use to access literature, particularly in the life sciences.

Some ECRs and students with sufficient support were able to transform experiences with unreliable literature into positive outcomes. Encouraging universities, institutions, and publishers to actively consider negative results (Bik, 2024) as integral components of publications or theses will help construct a positive culture around publication integrity. Furthermore, our results emphasise the need for institutions to go beyond superficial mandatory programs and offer more comprehensive education on

publication integrity, by addressing issues such as paper mills. As some participants noted, their education was often driven by self-interest or obtained outside institutional programs. The ECR demographic is motivated to sustain integrity (Abdi et al. 2021a, 2021b) and thus working with them when developing publication integrity education could create more satisfactory and practical education programs. Some topics of interest that we identified include the limits of acceptable research and motivations for publishing unreliable research. Furthermore, our findings suggest a hybrid approach to learning, where effective programs provide accessible resources and opportunities for discussion through didactic and discourse-focused educational methods. This is an area where future educational initiatives utilising AI chatbots (Kasani et al. 2024) or online forums could improve teaching about publication integrity, while maintaining the convenience of digital platforms.

4.4.5 Concluding remarks

In summary, publication integrity is a multi-factorial phenomenon with diverse impacts on ECR and student experiences that can either build them as better researchers or demoralise and demotivate them from pursuing academia. Considering this, we highlighted the need for further research to build on our findings about how ECRs and students are affected by publication integrity, and the need for systemic and cultural changes to encourage research environments of trust and safety.

Chapter 5: Discussion

5.1 Summary of major findings

The present thesis has identified three major findings. In chapter 2, we identified that 51% (60/118) of the original 2022 circRNA publications in high IF journals that we screened described incorrect nucleotide sequence reagents and/or problematic cell line identifiers. These features were also found in all retracted circRNA papers published in high IF journals between 2017 and 2021. In chapter 3, we found that the journals *Molecular Cancer* and *Oncogene* showed poor responses in publishing post-publication notices to address wrongly identified nucleotide sequences. We notified editors via email and then posted two groups of PubPeer comments, separated by 6 months, but PubPeer posts did not obviously affect editorial actions. This was also true in cases where the authors responded on PubPeer, declaring their intent to seek correction, yet no published correction addressing these errors occurred over the 9- and 15-month period of the study.

Finally, in chapter 4, we found that postgraduate research students and ECRs engage with publication integrity in three contexts: as consumers who read the literature, as contributors who build on scientific knowledge documented via publications and who also help to preserve publication integrity, and in an educational setting, where they learn about publication integrity. On one hand, some participants described positive contributions to encourage and preserve publication integrity by correcting the literature and ensuring that their publications are trustworthy and reliable. On the other

hand, some participants described being negatively impacted by unreliable literature, having experienced loss of time, resources, and funding due to being misled by unreliable publications. Some described experiencing negative emotions such as frustration and demoralisation, to the extent that they questioned the point of staying in academia. Together, this presented a concerning picture of the current research environment, where unreliable literature is common, and efforts to promptly correct the scientific record remain difficult. The presence of unreliable literature also has tangible impacts, such as wasted time and resources, and negative effects on the mental health of ECRs and research students.

5.2 Areas of research that show unexpected growth

Researchers from China and the USA authored 27% and 14% of all science and engineering papers published in 2022 (National Science Board & National Science Foundation, 2023). There was a sharp increase in the numbers of original circRNA papers from 2016 to 2021, largely by author teams solely located in China (Figure 5.1A). This trend was echoed in other ncRNA research, such as miRNA (Figure 5.1B) and lncRNA (Figure 5.1C) papers. This rapid growth in publication volume could be partly driven by advancements in sequencing and detection techniques, such as long-read RNA sequencing (Monzó et al., 2025). However, the growth in the number of ncRNA publications by authors in China is also surprising, given the lack of any socio-cultural factors that could have driven such outputs. For example, the sharp increase in COVID-19 publications (Figure 5.1D) was clearly in response to the pandemic, causing researchers across the globe to shift their focus to COVID-19 research. There

have not been similar developments that could obviously explain increased interest in research on ncRNAs.

Rapid publishing can invoke challenges, where some prominent COVID-19 publications were retracted, citing misconduct that could have been detected pre-publication (Mattoon et al. 2025). Our results in Chapter 2 highlight the persistence of uncorrected errors in circRNA papers in high IF journals. Fraudulent actors such as paper mills could be targeting ncRNA research (Byrne et al. 2022), or a snowballing effect could be created by the combined efforts of paper mills and genuine researchers, where rising numbers of ncRNA publications could be attracting genuine research interest.

When considering overall ncRNA publication numbers, it is interesting to note that the number of circRNA and lncRNA papers per year declined from peaks in 2021, and miRNA papers declined from a peak in 2020 (Figure 5.1A-C). Given the vast number of circRNAs available for study (Xu, 2017), it is unlikely that the circRNA research area is approaching exhaustion. Two reasons could explain these recent declines: paper mills could be losing interest in ncRNA topics, potentially in response to rising awareness of problems affecting the publication integrity of some human gene research (Byrne et al. 2022), and/or genuine researchers could be shifting away from pursuing ncRNA research. However, in saying this, there are still hundreds and thousands of circRNA, miRNA, and lncRNA papers being published per year, respectively (Figure 5.1A-C). These fields therefore remain active, highlighting the need for prompt correction of the scientific record to mitigate potential harms.

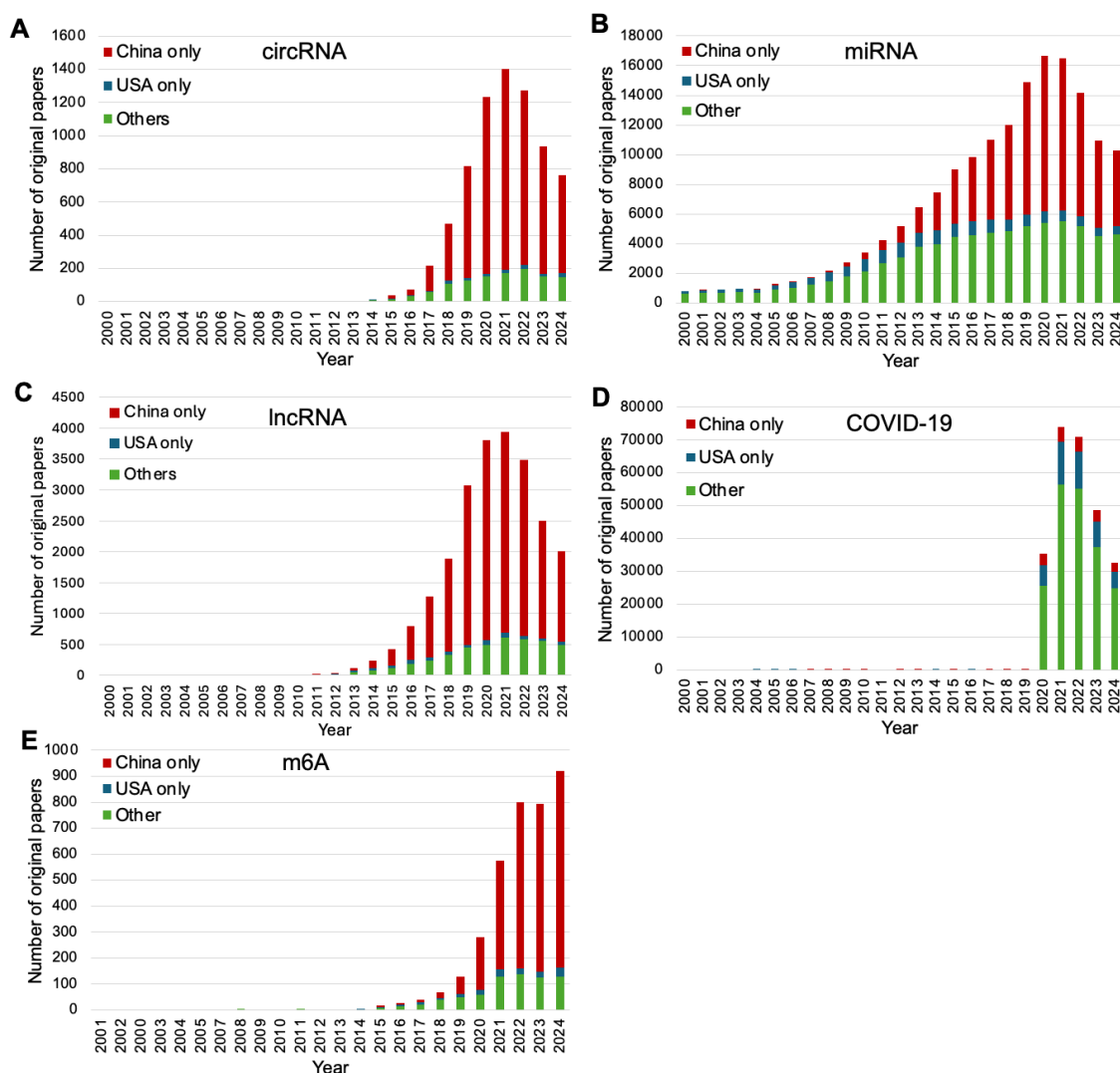


Figure 5.1. Number of original papers (Y-axis) across 2000-2024 (X-axis) according to Web of Science, for papers with A) circRNA ("circular RNA*", OR "circRNA*", OR "hsa_circ*" OR "hsa-circ*" OR hscirc* OR "circ* RNA*"), B) miRNA (microRNA*, OR miRNA*, OR miR* OR "hsa-miR*" OR "hsamiR*"), C) lncRNA (lncRNA* OR "long non-coding RNA*" OR "long non coding RNA*"), D) COVID-19 (coronavirus* or COVID*), and E) m6A (m6a* or "m 6a*") methylation in the title, according to country of origin (red = all authors from China, blue = all authors from USA, Green = all other affiliations, including papers with international teams). Papers by all authors from a single country were determined by excluding all other countries and selecting for a specific country on the countries/regions filter. The scale of the Y-axis is not uniform across the graphs.

Research paper mills are increasingly understood to be resilient enterprises that have been growing in capacity, in part by harnessing large networks of editors and authors (Richardson et al. 2025). A large number of papers have been recently found to reanalyse datasets such as the NHANES US national health dataset (Suchak et al., 2025) or large datasets of individual-level genotype data (Stender et al., 2024), where some papers describe misleading results or superficial and biologically inappropriate conclusions. Given the advent of generative AI, which has improved the capacity for anyone to build complex analysis pipelines, it is possible that paper mills may be shifting their approaches through secondary analyses of existing datasets (Spick et al., 2025). However, it seems unlikely that paper mills will completely change their business models, as doing so would require reconstructing existing infrastructure. Therefore, it is possible that some paper mills could be shifting their focus to new topics that add complexity to gene research.

Research topics with sharp increases in publications, particularly those that are mostly authored by researchers from one country or affiliation, should be carefully scrutinised. One possible area for further investigation is RNA methylation. In Pathmendra et al. (2024), four *Molecular Cancer* 2020 papers with incorrect nucleotide sequence reagents mentioned m6A in their titles (PMID 31906946, 32106857, 32429928, 32838807). We have since noticed rapid recent growth in publications about specific methylation modifications such as m6A (Figure 5.1E), where yearly publication numbers continued to increase in 2022-2024, when papers on ncRNAs were starting to decline. Together, this highlights a possibility that research paper mills may be now targeting the study of RNA methylation.

5.3 AI as both the poison and the panacea

5.3.1 Generative AI and publication integrity

AI has rapidly enhanced our capacity to process vast amounts of data (Duan et al., 2019), yet this capacity can be a double-edged sword—serving as a poison that exacerbates the publication integrity crisis or as a panacea that can help researchers uphold integrity. Generative AI can be used to produce experimental images, such as a micrograph of cells or Western blot bands (Zhu et al., 2024), create fake but realistic datasets de novo to support pre-determined conclusions (Taloni et al., 2023; Zhu et al., 2024), or generate text (Stokel-Walker, 2023). As such, there are justified concerns that generative AI could be harnessed by paper mills to produce manuscripts of superior quality (Jian and Yaeger, 2025; Liverpool, 2023). For example, image integrity issues such as image duplications and manipulations (Bik et al., 2016) are one of the base indicators of potentially paper mill-authored publications in molecular biology (Zhu et al., 2024). However, images produced through generative AI can be unique and so not easily detectable as duplications/manipulations by experts (Kwon, 2024). Paper mills could also harness the data-processing capacity of AI to produce superficial secondary data analyses of publicly available datasets (Spick et al., 2025). There is little doubt that AI could be used to bolster the publication quality of manuscripts authored by paper mills over quicker timeframes, giving rise to large numbers of manuscripts that may be difficult to detect as originating from paper mills.

Generative AI can also be leveraged to improve our capacity to detect unreliable literature at scale. For instance, AI-powered image detection software such as

ImageTwin, Proofig AI, FigCheck, and ImaCheck have capacities where they are now outperforming human experts at detecting manipulated images (Jian and Yaegar, 2025; Oza, 2023). Proofig was also reported to be capable of detecting AI-generated images in manuscripts (Kwon, 2024). There have been attempts to build AI-based software to detect AI-generated text or embed watermarks in content created through generative AI (Jian and Yaegar, 2025). As such, AI holds many possibilities to serve as a panacea to the publication integrity crisis, bolstering our capacity to detect unreliable literature, and particularly paper-mill authored publications.

5.3.2 How generative AI could change engagement with the literature

AI-powered tools can rapidly summarise and process information, yet it has been recognised that continued over-reliance of AI, especially amongst younger users, can degrade critical thinking skills (Kosmyrna et al., 2025). According to Thomson et al. (2024), 48% of higher education students recalled using AI to summarise information, 42% used AI to paraphrase information, and 46% students also recalled using AI to clarify their understanding of content (Thomson et al., 2024). This reflects how AI is becoming integral to how students read, consume and process information.

We asked ChatGPT-4.0-turbo to summarise and assess the reliability of PMID 35354791, a circRNA study that described experiments in three contaminated cell lines and the use of three incorrectly identified nucleotide sequence reagents (Figure 5.2). However, when we asked ChatGPT to summarise the significance of the study,

the output did not mention issues in methodology or reliability that could affect the validity of the study's conclusions. It is only when we asked ChatGPT to assess whether the source is trustworthy that the AI responded addressed this question (Figure 5.2). It is concerning that the AI on this occasion did not recognise the reagent errors that our analysis uncovered (Chapter 2, Supplementary Tables 3.2, 3.3). In addition, current large language models like ChatGPT cannot process images, and thus are limited in their capacity to evaluate image integrity in publications. This failure to address quality issues was also noted by Thelwall et al. (2025), who asked ChatGPT 4o-mini to evaluate the quality of 217 retracted articles, only to find that none of the outputs mentioned that the articles were retracted or had errors.

Can you please summarise the paper "Hsa_circ_0007967 promotes gastric cancer proliferation through the miR-411-5p/MAML3 axis" in a short paragraph in terms of its significance

The study "Hsa_circ_0007967 promotes gastric cancer proliferation through the miR-411-5p/MAML3 axis" investigates the role of the circular RNA **Hsa_circ_0007967** in gastric cancer (GC). The researchers found that this circRNA promotes the proliferation of GC cells by acting as a **miR-411-5p** sponge, which subsequently increases the expression of **MAML3**, a key regulator involved in the **Notch signalling pathway**. This discovery highlights the potential of Hsa_circ_0007967 as a novel biomarker and therapeutic target in gastric cancer, offering insight into the complex molecular mechanisms driving tumour growth and progression. The study is significant as it identifies a new regulatory axis that could be exploited for developing targeted treatments or diagnostic tools for GC.

Based on your access, would you trust this? Explain in a paragraph.

The paper published in *Cell Death & Disease*, a reputable peer-reviewed journal under *Nature Research*, suggests a high level of reliability. The journal's rigorous editorial process and the paper's focused exploration of the *miR-411-5p/MAML3 axis* in gastric cancer add credibility to its findings. However, to fully trust the study, it's important to review its methodology—ensuring appropriate controls and reproducibility. While the publication itself is credible, further validation in multiple models and citation by other independent studies would strengthen its reliability. Overall, based on the journal and topic, the paper appears trustworthy, but a deeper look at the experimental details would be wise for full confidence.

Figure 5.2. Summary of the response made by GPT-4.0-turbo to queries about PMID 35354791. Black boxes represent input queries, while green boxes represent responses from ChatGPT. This was performed on 15th August, 2025.

This exercise highlights two concerning aspects of AI use: firstly, when asked to summarise information, the AI failed to critically appraise it; secondly, the responses to assessing trustworthiness emphasised the source's reputation, potentially encouraging students and researchers to trust publications based on superficial measures like IF or journal reputation. There have also been recommendations to use AI language models for the analysis of literature trends at scale to aid policymakers and R&D managers with funding decision-making (Lobanova et al., 2023). For example, Lobanova et al. (2023) used an AI language model to assess trends across publications in Life Science journals between 2010 and 2019, identifying circRNA research as a mainstream trend that is a popular area of study and practical application. This is concerning in light of our observations in Chapter 2, where many circRNA papers in high IF journals showed problematic features. The inability of AI tools, such as ChatGPT, to critically appraise information (Figure 5.2), combined with an inefficient post-publication correction system (Chapter 3), creates a potentially harmful situation. We also identified vulnerable students and ECRs who hold implicit trust in the scientific literature or have wasted resources and time due to unreliable publications (Chapter 4). It is therefore reasonable to speculate that AI could lead to increased uptake of unreliable literature by researchers and the broader community, with a range of potential consequences that we cannot fully predict.

5.4 Solutions – what can we do?

With respect to solutions, there are two major approaches: we can enable more efficient post-publication corrections to preserve the integrity of the scientific record,

and we can educate researchers to be more capable of distinguishing reliable literature from its unreliable counterparts. Ultimately, both approaches will be required.

Prompt post-publication editorial actions on unreliable literature could minimise their presence within the literature and block them from being built upon by researchers and used as training information for AI. Journal editors in salaried roles could play a key role in this regard, as they are well placed to enforce more rigorous approaches during initial manuscript screening. Platforms such as PubPeer have been leveraged to make comments on unreliable papers (Caron et al., 2024; Townsend, 2013), yet, as identified in Chapter 4, few research students and ECRs may be aware of the PubPeer platform. Reopening PubMed Commons, a platform previously linked to the most widely used biomedical publication search engine (Dolgin, 2018), could be more effective in ensuring that the broader community is aware of concerns identified post-publication (Byrne and Barnett, 2024). Alternatively, integrating information about PubPeer and the associated plugin (Barbour and Stell, 2020) into education programs could raise awareness of the availability of PubPeer, and thus, more researchers could use this resource to navigate the literature.

As identified in Chapter 4, well-rounded education in publication integrity beyond tokenistic coursework can help researchers to build the knowledge necessary to critically engage with the literature and navigate any presence of unreliable literature. One such knowledge source that could be integrated into education is COSIG, an open resource with 30 guides that provide domain-specific knowledge to support post-publication peer review (Richardson, 2025). Furthermore, as described in Chapter 4,

education focused on discourse-oriented forms and experiential learning targeted towards building skills in evaluating the literature or conducting reproducibility experiments could build more critically aware researchers, less likely to be misled by unreliable literature. Another possibility is the use of chatbots to aid critical thinking (Fabio et al. 2024), where helper bots could ask key questions concerning reliability and provide additional information, such as whether the paper has PubPeer comments or has been cited as being potentially unreliable. We could integrate other resources, such as COSIG (Richardson, 2025) into this helper bot to help readers navigate the literature in a more critical manner, thereby mitigating harms posed by unreliable literature.

5.5 Concluding remarks

In summary, this thesis presents worrying data concerning biomedical publication integrity, where inaction is perhaps the most dangerous action of all. We have identified emerging fields of research contaminated with papers of poor publication integrity, the lack of prompt post-publication correction capacity and how research students and ECRs navigate the publication integrity in varying contexts. Education, awareness and in-depth knowledge of publication integrity are essential to navigate the literature safely and reduce the risks of engaging with unreliable sources. Despite the recognised crisis in publication integrity, there are also encouraging signs, such as growing interest in efforts to uphold publication standards that require further support. As researchers, it remains our duty to uphold publication integrity and correct the scientific record, ensuring that science remains reliable and trustworthy for others.

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Appendices

All supplementary tables are available as separate excel files. Supplementary File 1. is available on p286.

Supplementary Table 1.1. Wrongly identified nucleotide sequences in *Molecular Cancer* and *Oncogene* papers with circRNA sequence reagents

Supplementary Table 1.2. Overview of *Molecular Cancer* and *Oncogene* papers with wrongly identified and/or non-verifiable nucleotide sequence reagents

Supplementary Table 1.3. Non-verifiable sequences identified in *Molecular Cancer* and *Oncogene* papers with circRNA sequence reagents

Supplementary Table 2.1. Overview of retracted circRNA paper published in journals with high impact factor.

Supplementary Table 2.2. Wrongly identified nucleotide sequences identified in retracted circRNA papers published in journals with high impact factor

Supplementary Table 2.3. Non-verifiable nucleotide sequences identified in retracted circRNA papers published in journals with high impact factor.

Supplementary Table 2.4. Problematic cell lines identified in retracted circRNA papers published in journals with high impact factor.

Supplementary Table 3.1. Overview of 2022 circRNA papers published in high impact factor journals collated via search strategy on Web of Science that were A) excluded or B) included in analyses

Supplementary Table 3.2. Wrongly identified nucleotide sequence reagents were identified in 2022 circRNA papers published in high impact factor journals.

Supplementary Table 3.3. Overview of incorrect 2022 circRNA papers published in high impact factor journals with at least one wrongly identified nucleotide sequence reagent and/or problematic cell lines.

Supplementary Table 3.4. Overview of circRNA papers with all correctly identified nucleotide sequence reagents and cell lines published in 2022, high impact factor journals.

Supplementary Table 3.5. Summary of the disease focus of the incorrect circRNA, 2022 circRNA papers published in high impact factor journals with at least one wrongly identified nucleotide sequence reagent or problematic cell lines.

Supplementary Table 3.6. Non-verifiable nucleotide sequences identified in 2022 circRNA papers published in high impact factor journals.

Supplementary Table 3.7. Summary of FISH/ISH, RNA-pull down probes predicted to target claimed circRNA according to nucleotide identity shown across the BSJ.

Supplementary Table 3.8. Problematic cell lines identified in 2022 circRNA papers published high impact factor journals.

Supplementary Table 3.9. Non-verifiable cell lines identified in 2022 circRNA papers published in high impact factor journals.

Supplementary Table 4.1. Summary of the incorrect *Molecular Cancer* and *Oncogene* papers identified in Pathmendra et al. (2024) and corresponding PubPeer posts made prior to and during the study (April 2023-July 2024).

Supplementary Table 4.2. Overview of wrongly identified nucleotide sequence reagents in *Molecular Cancer* and *Oncogene* papers identified in Pathmendra et al. (2024) that were addressed via PubPeer and/or published correction

Supplementary File 1. Survey Questions

Demographic Questions

1. What is your gender?
 - a. Male
 - b. Female
 - c. Other
 - d. Prefer not to say

2. What is your age?
 - a. Less than 25
 - b. 25–30
 - c. 31–35
 - d. 36–40
 - e. 41–45
 - f. Over 45
 - g. Prefer not to say

3. Which country are you located in?
 - a. Drop down box for country

4. Is English your first language?
 - a. Yes
 - b. No
 - c. Prefer not to say

5. What is your primary scholarly/research discipline, defined as the discipline in which you are the most active?
 - a. Arts & Humanities
 - b. Life Sciences & Biomedicine
 - c. Physical Sciences
 - d. Social Sciences
 - e. Technology [including engineering, and information technology]
 - f. Other [open text with limited phrase]

6. What is your current research career stage?
 - a. Undertaking a Masters
 - b. Undertaking a PhD or equivalent
 - c. 1-3 years post-doctoral degree
 - d. 4-7 years post PhD?
 - e. 8-10 years post PhD?
 - f. Other [open text box]

Topic Questions

1. Please explain how you would define “reliable literature” in your discipline?
 - a. Open text box

2. “I find the existing literature in my discipline to be generally reliable”. How would you respond to this statement?
 - a. Strongly Disagree
 - b. Disagree
 - c. Neutral
 - d. Agree
 - e. Strongly Agree

3. What helps you to decide whether a published peer reviewed finding in your discipline is **reliable**? Please select all that apply:
 - a. Journal impact factor of the publication
 - b. The publication is highly cited
 - c. The publication was recommended by supervisor(s)
 - d. The publication was recommended by colleague(s)
 - e. The publication was recommended by a trusted research group
 - f. The published finding is consistent with previous publications
 - g. The publication has a protocol
 - h. The publication was pre-registered
 - i. Other [open text box]

4. Please recount (if any) experience(s) you have had with unreliable publication(s) in your discipline. If you have no experience with unreliable publications, please state this in your response and go to question 7.
 - a. Yes – Please briefly recount your experience(s) below [open text box]
 - b. No

Q5 and Q6 only available to those who responded yes to Q4

5. Please outline how you responded to the unreliable publication(s) that you encountered in your discipline.
 - a. Open text box

6. Briefly recount any impact of unreliable publication(s) on your research, career, and/or personal well-being. If you have experienced no impact, please state this in your response.
 - a. Open text box

7. Are you aware of research paper mills?
 - a. Yes [lead to sub-questions if participant selects 'Yes']
 - i. How did you gain awareness of paper mills? [open text box]
 - ii. Please explain whether you believe that paper mills are active in your research discipline. [open text box]
 - b. No [Optional open text box for participant to clarify]

8. Are you aware of PubPeer?
 - a. Yes [lead to sub-questions if participant selects 'Yes']
 - i. What do you know about PubPeer? [open text box]
 - ii. How did you learn about PubPeer? [open text box]
 - iii. Please briefly describe (if any) your experience with using PubPeer [open text box]
 - b. No [Optional open text box for participant to clarify]

9. Have you ever attempted to reproduce a published finding?
 - a. Yes [Go to Question 10]
 - b. No [Optional open text box to clarify, go to Question 12]

10. Have you ever encountered published findings that you could not reproduce?
 - a. Yes [lead to sub-questions if participant selects 'Yes']
 - i. Please briefly outline your experience with the irreproducible findings including the process of following up the published result. [open text box]
 - ii. Please briefly recount any impact on yourself (for example, on your research, career, or personal well-being). [open text box]
 - b. No [Optional open text box to clarify]

11. "If a finding is irreproducible, I am likely to believe that this represents a fault on my part rather than a problem with the published finding".
 - a. Strongly Disagree
 - b. Disagree
 - c. Neutral
 - d. Agree
 - e. Strongly Agree

Please outline your reasoning for your response.

- a. Open text box

12. During your research training or career to date, have you learned about publication integrity?
- a. Yes [lead to sub-questions if participant selects 'Yes']
 - i. How have you learned about publication integrity? [open text box]
 - ii. Please briefly outline your reasons for learning about publication integrity. [open text box]
 - b. No [Optional open text box for participant to clarify]
13. During your research training or career to date, have you learned about how to reproduce published findings?
- a. Yes [lead to sub-questions if participant selects 'Yes']
 - i. How did you learn these skill(s)? [open text box]
 - ii. Please describe whether you found these methods of learning to be effective. [open text box]
 - b. No [Optional open text box for participant to clarify]
14. To what extent do you agree with the following statement: "I am confident in my ability to identify unreliable publications in my discipline".
- a. Strongly Disagree
 - b. Disagree
 - c. Neutral
 - d. Agree
 - e. Strongly Agree

Please briefly outline your reasoning for your response

- a. Open text box
15. If you suspect a publication was unreliable, who would you first discuss the issues with?
- a. Nobody
 - b. Colleague at my level
 - c. Senior colleague
 - d. The paper's authors
 - e. My research integrity office
 - f. Other [open text box]
16. Please describe what more you would like to learn about publication integrity, if anything?
- a. Open text box

17. How would you like to receive education about publication integrity? Please select all that apply:

- a. Lectures – online
- b. Lectures – in-person
- c. Pre-recorded lectures
- d. Discussion group – online
- e. Discussion group – in person
- f. Online forum
- g. Reading material
- h. I don't need further training in publication integrity
- i. Other – please specify [open text box]

Please briefly outline your reasoning for your response

- a. Open text box

Final questions

18. Is there anything else you would like to add that we didn't ask about?

- a. Open text box

19. Would you like to be contacted by a member of our research team about any of your responses through an interview or focus group?

Please note: your identified details will be in a separate form and not linked to any responses you have made so far in this survey.

- a. Yes [separate form to collect identifiable details]
- b. No [close survey: We thank you for your time spent taking this survey. Your response has been recorded.]