Genetic counselling: genomic uncertainties

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Abstract

Genomic sequencing technologies are increasingly used in health. Improvements in sequencing technology and reductions in its cost mean that the default approach is frequently to obtain more genomic information rather than less. However, the volume of genomic data does not necessarily track with its ability to be interpreted, and it is widely acknowledged that genomic sequencing can increase, rather than resolve, uncertainty for patients and their families. Uncertainty in genomics impacts both professionals and patients. The near certainty of uncertainty should be factored into all elements of the genetic and genomic testing process, from initial test offer to longer-term follow-up. In some circumstances, uncertainty can provide a valid reason to restrict the scope of testing. Given its resource implications, uncertainty in genomics should also be considered at the health system level. Ethical provision of genomic sequencing in health-care necessitates both planning for uncertainty and minimising its impact on all stakeholders.

Keywords

Uncertainty, Genetics, Genomics, Genetic Counselling, Ethics, Genetic testing, Hype, DNA sequencing

Key concepts

- The integration of genetic and genomic testing into various medical specialties is increasing, making genetic information more accessible to patients.
- Despite technological advancements, genetic and genomic testing often introduces new uncertainties.
- Different dimensions of uncertainty in genomics include its sources (probability, ambiguity, complexity), issues (scientific, personal, practical) and loci (patients, providers, policymakers).
- Patients and their families may experience emotional and psychological impacts due to uncertain or unexpected results from genetic and genomic tests.
- Genetic counsellors play a crucial role in helping patients understand and cope with the uncertainties and implications of genetic and genomic testing.
- Ethical responses to genomic uncertainty involve promoting resilience, patient welfare, autonomy and solidarity, while managing expectations and providing support.
- Ethically responding to uncertainty also requires considering uncertainty at all stages of the testing process, including decisions on whether to undergo testing and whether or how to disclose uncertain information.
- Inherent uncertainties in genomic testing need to be considered in all settings where genomic information is offered, not just clinical care.
- Managing genomic uncertainty effectively is essential for the sustainability and stability of health systems, including considerations of resource allocation and environmental impact.
- The volume of genomic data does not necessarily correlate with its interpretability, and this should be factored into the genetic and genomic testing process from initial test offer to long-term follow-up.

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Introduction

Advances in DNA sequencing technologies, decreases in costs and the rapid uptake of genetic testing in clinical disciplines other than genetics (also known as 'mainstreaming') are all contributing to more genetic information being obtained from more patients than ever before. In cancer care, for example, it is becoming routine to seek to identify a genetic cause of a patient's cancer by offering genetic testing, and doing so through large gene panels. Other drivers, such as better engaging patients and consumers in health system design and policy, an increasing commercial presence in the genetic testing landscape and general enthusiasm for, and beliefs in the value of, testing and information, all mean that genetic and genomic testing will play an increasing role in health-care delivery, research and population health. However, genetic and genomic testing may not always provide its recipients with an answer, and it may return unexpected results.

When new 'next-generation' DNA sequencing technologies were introduced over a decade ago, initial expectations (among both health professionals and patients) were that these technologies would resolve uncertainty more often than not. However, when advanced sequencing technologies began to be deployed in healthy people (e.g. to help build variant interpretation databases), it was observed that many of these individuals also had genomic variants that were thought to cause disease (Kingdom and Wright, 2022). Rather than resolving uncertainty, advanced sequencing technologies introduce many new opportunities for, and dimensions of, uncertainty (Barlow-Stewart, 2018; Pyeritz, 2017). See also: Genetic Counseling Consultations: Uncertainty

In this chapter, we discuss how the genetic and genomic testing landscape can be transformative for patient care, but that it can also raise new uncertainties. We begin by describing genetic and genomic testing, before moving on to discuss how uncertainty can arise in such tests. We then define and unpack genomic uncertainty in more depth, and synthesise some of the research regarding how patients and professionals manage and cope with uncertainty in genetic and genomic testing. We end by providing a view on how uncertainty in genetics and genomics should be responded to, including some points for practice. We posit that uncertainty is inherent to genomics and should be consciously embraced and explicitly accounted for at all stages of the testing process. With this, offers of genomic information can uphold key ethical concepts including promoting resilience and acting in solidarity with patients and providers.

Genetic and Genomic Testing

Genetic and genomic testing, and the related offer of genetic counselling, have expanded significantly in recent decades. Broadly speaking, a *genetic* test is one that looks at a single gene, or a few genes, in a patient. A *genomic* test is one that looks at a large number of

genes, or the entire exome or genome, of a patient. Whether the test is genetic or genomic, most tests nowadays draw on technologies based on so-called 'next-generation' DNA sequencing. This type of testing, which generally generates a large amount of data for subsequent interpretation, is characterised by being fast ('high throughput'), inexpensive and increasingly accurate, enabling longer and longer 'reads' of the genome at greater and greater 'depth' (i.e., the number of times a particular base pair is 'read').

With these advances in sequencing, genetic and genomic testing can in principle be offered at a range of times throughout a person's life (i.e., before birth, in infancy or childhood, or in adulthood). Mainstreaming has seen offers of genetic and genomic testing become increasingly prevalent in nearly all specialities of medicine (e.g. in paediatrics, obstetrics, neurology, cardiology and oncology), as well as use in other non-clinical domains such as adoption (Arribas-Ayllon *et al.,* 2022), and via direct to consumer genetic testing.

Genetic and genomic tests are also realised through many different types of tests, most of which seek to analyse the germline genetic makeup of an individual (i.e., the gene variants present in all or nearly all the cells of the body), although some tests are designed to detect somatic genetic changes (e.g. testing a tumour sample). These tests can evaluate a single gene, many genes that cause related conditions (e.g. a gene-panel addressing conditions with intellectual disability, or a cancer predisposition gene panel), or may sequence the exome or whole genome of an individual.

Genetic and genomic tests can be performed diagnostically, meaning the goal is to find a diagnosis for primary features that have been clinically identified, such as an exome sequence to identify a genetic cause for a child's intellectual disability, congenital heart defect and other medical features, or a cancer gene panel to identify whether there is a genetic cause to a person's early onset cancer. Or, a test can be done predictively to identify future genetic risks, for example to determine whether a person has inherited a familial variant in an early-onset dementia gene.

As noted above, next-generation sequencing enables high-throughput sequencing of the genome, as well as the ability to generate and apply large gene panels (groups of variants). This means that it is possible to examine and interpret more of the genome than ever before, at increasingly reduced cost. Improvements in cloud-based storage also mean that this data can, at least hypothetically, be stored for further examination and re-interrogation over time.

This ability to look at more of the genome means that genomic testing now routinely tends to look for more rather than less. For example, in cancer care there is now a tendency to construct and use larger panels for familial cancer predisposition testing. In several settings globally, secondary or additional findings (i.e., findings that may be relevant to a patient's health but which are beyond the initial test indication) can be searched for at the time of testing. And for some test types (and depending on the health setting), findings that may comprise a variant of uncertain significance (VUS; see Glossary) may be returned. See also: See also: Management of Incidental Findings in Clinical Genomic Sequencing Studies; Ethical Issues in Multiplex Genetic Testing.

Uncertainty in Genetics and Genomics

Genomic testing is often sought in the hope that it will reduce uncertainty (e.g. Arribas-Ayllon *et al.,* 2022; Barlow-Stewart, 2018). Yet as Han and colleagues note: 'Genomic technologies introduce uncertainties of unique scales and types' (Han *et al.,* 2017). One test can also lead to further tests, creating additional uncertainties. While genomics is a powerful health technology and is one which has significantly improved diagnostic yield (particularly in the rare disease setting), it is, and will remain, inherently intertwined with uncertainty (Howard and Iwarsson, 2018).

In a general sense, 'uncertainty' can be defined as the "conscious awareness of ignorance - a self-awareness of incomplete knowledge of some aspect of the world" (Han *et al.,* 2017), or "a state of having imperfect or unknown information." (Newson *et al.,* 2016). That is to say, there are two elements at play when something is uncertain: (1) that information is imperfect, incomplete or unknown and (2) that a person (whether a patient or a provider) is aware that information has this property.

Within genomics, uncertainty has been described as:

> '...a status quo that arises when information that is obtained from genomic testing is imperfect or unknown, leading to uncertainty in clinical diagnosis or management.' (Newson *et al.,* 2016)

Uncertainty is inherent to genetic and genomic tests, as sequencing techniques remain subject to limitations (Horton and Lucassen, 2019). First, regardless of which type of test is performed, genomic information often remains a poor predictor of overall human health. We do not yet (and may never) understand what much of the human genome does, and the mere generation of genomic data does not automatically enable its interpretation into health information that is meaningful for people. Even when a genetic or genomic test 'finds an answer,' there is frequently prognostic uncertainty around what a genetic condition will 'look like' (its expression), and whether and when it will present (its penetrance and age of onset). These predictions are particularly challenging in situations like prenatal genomic testing, when even less is known about the natural history of many diagnosable genetic conditions (Lewis *et al.,* 2022).

Another area of genomic uncertainty relates to the clinical impact of variation in newly discovered genes ('genes of uncertain significance') and variants that are not fully understood ('variants of uncertain significance', or VUS). Variants are changes from the expected genome, some of which are pathogenic (i.e., disease-causing) or likely pathogenic, while others are benign. Since most variants are identified in patients only infrequently, it is often not clear whether they are medically impactful. Such variants may have unclear clinical validity, including regarding their natural history, expression or penetrance. Time and additional data, including broader genomic data sharing and functional assays (tests) will be required to provide better variant interpretation and minimise the number of initial VUS results that are reported (Fowler and Rehm, 2024).

Another aspect of genomic uncertainty is that some variants once thought to be pathogenic have subsequently been identified in healthy people (Kingdom and Wright, 2022). This has particularly been the case in people whose ancestry is not well represented in genomic interpretation databases (Manrai *et al.,* 2016). Such databases do not yet reflect population diversity, although this situation is improving (Burke, 2021). In the meantime, however, it bears noting that genomic uncertainty disproportionately impacts people who already experience structural inequalities or health disparities (Madden *et al.,* 2024; Popejoy and Fullerton, 2016).

Taxonomies of Genomic Uncertainty

Uncertainty has been discussed for some time in the medical communication, medical decision-making and nursing literature. Within this, various taxonomies of uncertainty have been proposed (Han *et al.,* 2011). In genomics, the best-known and most widely applied taxonomy of uncertainty has been developed by Han *et al.* (2017) (Figure 1). This account of uncertainty, which builds upon and adapts previous taxonomies of uncertainty, has three 'dimensions': the source of uncertainty, the issues arising from it and the loci in which the uncertainty is found.

The **source** of uncertainty means its cause or origin. Han *et al*. (2017) describe three types of sources of uncertainty in genomics: probability, ambiguity and complexity. Probability picks up on the inherently indeterminate nature of much genetic and genomic testing (as is the case with many other medical tests). Ambiguity draws on the lack of reliability of some information used in interpreting genomic test results. Han *et al.* subdivide this source further into ambiguity in concepts (e.g. how a condition is classified), ambiguity in methods such as variant interpretation, and ambiguity arising in the clinic such as gaps in family history or other clinical information that would be necessary to help patients obtain greater certainty in genomic testing. Complexity as a source of uncertainty picks up on features of genomic information that can challenge our understanding of it. As we have noted above, there are numerous features of genomic information that can make it complex. One element is how a genetic condition is caused. While many genetic conditions are caused by a change in a single gene, still others occur due to variants in several genes, either working together or independently. Another element is the effect or impact of a genetic variant. Han *et al.* use the example of pleiotropy to illustrate this: one gene can impact more than one phenotype. Complexity also arises from what Han *et al.* call 'effect modification': genes interact with not only each other but also their environment to impact health. Altogether, Han *et al.'s* taxonomy illustrates that there are many dimensions to the sources of uncertainty.

The **issue** of uncertainty refers to the types of substantive situation that uncertainty gives rise to, that is, scientific, personal and practical uncertainty. Scientific uncertainty in genomics refers to issues that arise during diagnosis, such as making predictions on the basis of information obtained, determining why a condition arose in a particular patient and what treatment or mitigation strategies might be available. Personal uncertainty draws attention to the impact of uncertainty on patients (see further below), such as how it might

play a part in a person's well-being and relationships. Practical uncertainty refers to the wider health system context in which the uncertainty arises. This includes aspects such as the availability of resources and procedures necessary for genomic testing to be offered.

Finally, the **loci** of uncertainty describes in whom it rests, such as the patient, the laboratory, the clinician or researcher, or the policymaker. The needs and interests of these stakeholders will vary; for example, patients will be more interested in the practical impact on their and their family's health, while a policymaker will be more concerned with the wider implications of genomic testing (including its ethical, legal and social aspects) and its health system implementation.

In presenting their comprehensive taxonomy, Han *et al.* (2017) argue that a full appreciation of uncertainty in genomic medicine, such as the one gained by working through their taxonomy, is important in order to avoid being ignorant of some forms of uncertainty. Having this appreciation of uncertainty is also an important aspect of promoting goals such as shared decision-making in clinical practice.

There is a further distinction in genomic uncertainty, developed in the context of returning secondary/unsolicited/additional findings: that between non-normative uncertainty and normative uncertainty (van der Schoot *et al.,* 2024) Non-normative uncertainty describes all empirical (fact-based) aspects of test-related uncertainty, while normative uncertainty points to the possibility or actuality of a moral conflict arising from uncertainty. Normative uncertainty cannot be resolved even if there is perfect or certain information. Both kinds of uncertainty should be considered and addressed during the testing process.

The Impact of Genomic Uncertainty on Patients and Providers

In both clinical and research settings, patients, research participants and their families often report perceiving uncertainty around genetic and genomic testing results, and these responses map well to the taxonomy of uncertainty described above. As Kuiper *et al.* (2023) note, uncertainty can have a dual nature: it can be both burdensome and productive. Uncertainty may pose a challenge to moving forward following genetic or genomic testing, but it can also form a basis for discussion and collaboration - between health professionals, or between patients and their care providers (Kuiper *et al.,* 2023). Patients respond differently to uncertainty depending on factors such as their information-seeking preferences, their general optimism, their past experiences with genetic or genomic testing and their ambiguity tolerance (Richardson and Ormond, 2018). Hope is also used by patients when responding to uncertainty (Neustadt *et al.,* 2020).

With genomic testing, there is often the perception that 'knowledge is power' and that more information will always be helpful, or provide clarity. Because of this, patients can feel pressure to accept genomic tests, or to agree to receive 'add on' information for tests that they are already having (Bernhardt *et al.,* 2013). They can then struggle when they don't really understand their results or when they receive uncertain information (Hillman *et al.,*

2013; Reyes *et al.,* 2021; Walser *et al.,* 2015), which can impact both their ability to make decisions and their emotional well-being (Biesecker *et al.,* 2014). For example, pregnant persons might receive unclear or contradictory prenatal testing information and feel shocked or anxious about what to do (Bernhardt *et al.,* 2013). Parents whose infant receives inconclusive newborn screening results may feel uncertain about whether their child is affected (Boardman and Clark, 2022). An adult found to carry a pathogenic variant in *BRCA1* could voice uncertainty about whether or when they might get cancer (Bradbury *et al.,* 2016).

Not only is uncertainty impactful for patients and families; we also know that uncertainty is felt by medical providers. Both patients and providers can feel a bit helpless in uncertain situations (Richardson and Ormond, 2018; Werner-Lin *et al.,* 2016). For medical providers, this can make them feel uncomfortable, and unsure what to share with patients (Bernhardt et al., 2014; Walser et al., 2015). There is also diversity in the manifestation of uncertainty in genomics among providers. Kuiper *et al.* (2023) discuss how uncertainty is experienced and practised differently by clinicians and laboratory practitioners. For a laboratory scientist or genetic pathologist, uncertainty may have more to do with how a test is performed - are the methods accurate? Is the analysis complete? There may also be a mindset to keep looking at data in order to resolve uncertainty or find an answer. Clinical geneticists (and, we'd add, genetic counsellors), in contrast, tend to think about uncertainty in relation to their patients. They are keen to resolve uncertainty for the people for whom they provide medical care and want to ensure that they are reporting information that will be relevant to, and helpful for, the patient.

In response to early descriptive studies on genetic uncertainty, Biesecker *et al.* (2017) developed and validated the Perceptions of Uncertainties in Genome Sequencing (PUGS) scale. This scale measures clinical, affective and evaluative uncertainties in genetic and genomic testing. PUGS has now been used in multiple studies to examine not only how individuals respond after genetic testing, but also to consider how perceptions of (and tolerance of) uncertainty drive hypothetical interest in genetic tests (e.g. Bartley *et al.,* 2021; Ratcliff *et al.,* 2021; Zhong *et al.,* 2023).

Ethically Responding to Uncertainty

In developing an 'ethics of uncertainty' for genomic medicine, Newson *et al.* (2016) argued that it is important to challenge the notion that genomic testing always reduces or eradicates uncertainty. Doing so requires both recognising the current limits to genomics (outlined above) and also mitigating hype [i.e. a distorting effect caused by 'the tendency to exaggerate the value of near-future application of research results' (Caulfield, 2016)]. It is also important to recognise that uncertainty can be linked to hope or optimism, as described above. That is, uncertainty is not necessarily nefarious.

Newson *et al.* (2016) also suggested a number of ethical concepts that may be useful when acting ethically regarding genomic uncertainty: resilience, welfare, autonomy and solidarity. While space constraints preclude us from expanding on them in depth, resilience involves

preparing individuals and health systems to cope with the inherent uncertainty of genomics and to build both psychological and systemic strategies to manage it well. Promoting the welfare of patients is also key and will necessitate considering the psychological impact of uncertain results and providing support when its negative effects may be observed. Promoting patient autonomy requires that patients are given space and support to make decisions in line with their values, including the place of uncertainty within this. Finally, solidarity necessitates that we act collectively to support all who face the uncertainties of genomic information and to engage from a position of understanding and empathy (Newson *et al.,* 2016).

While existing scholarship on ethics and uncertainty is a helpful addition to the literature, gaps remain. There are at least five areas that require further inquiry: ethical preparedness for uncertainty, determining disclosure, considering non-clinical settings, focusing on families and thinking at a systems level.

Ethical preparedness for uncertainty

Most existing scholarship on uncertainty considers it at the point of responding to the results of genomic testing. On this approach, a consideration of uncertainty will only become relevant once a result exists. Uncertainty and its management are considered as a response, with anticipatory and upstream uncertainty considerations neglected. To change this, uncertainty should be considered at all points of testing, including a decision over whether a test is, all things considered, indicated. This appraisal should also recognise not only that there are some forms of uncertainty that it is desirable to reduce or mitigate as part of the counselling and testing process, but also that there are other types of uncertainty that may be framed as a source of options and hope for the future.

Determining disclosure

Related to the first point, existing scholarship on uncertainty - and its attendant focus on managing results - tends to assume both that testing will take place and that if it does, uncertain information will be disclosed. Instead, an appraisal of uncertainty, including its tolerance, could form part of the process of shared decision-making to determine whether to undergo a test. It should also, as Han *et al.* (2017) argue, inform deliberation about 'how broad and deep' to go into uncertainty with any given stakeholder. Further, it is worth noting that in some settings, such as population-scale reproductive genetic carrier screening, it has been argued that returning uncertain information is not ethically justified (Righetti *et al.,* 2022).

Considering uncertainty in settings other than clinical care

As genomic testing develops and expands, it is being deployed in settings other than clinical care. For example, there are pilot studies underway in many countries to consider how genomics could be used in population screening programs such as newborn screening (Stark and Scott, 2023). There are also trials or pilot programs to offer genomic testing to healthy adults or programs to offer carrier testing at population scale to inform reproductive

decision-making (Kirk *et al.,* 2024). Yet to date the uncertainty literature, including its ethical consideration, has predominantly focused on clinical care. Ongoing considerations of the ethics of uncertainty need to expand to consider the role that uncertainty should play in the design and offer of genomic testing beyond the clinical setting.

Involving families

Most theoretical and empirical work on uncertainty to date has considered the place of uncertainty in the context of the professional/patient relationship. Yet, genetic information is shared within families and so when uncertainty arises this may also be experienced by other family members. The existing predominant focus on uncertainty within a patient/physician dyad needs to be expanded to consider uncertainty at the level of families and the community. This also recognises scholarship on autonomy that embraces a relational dimension, seeing ties between people not as constraining but as potentially enriching of autonomy.

Thinking at systems level

It is important to consider the role that the inherent uncertainty of genomic information will play in determining how to offer genomic testing in complex health systems. Reporting uncertainty generates considerations beyond the patient-clinician dyad. For example, the collective impact of multiple appointments to discuss and follow up on uncertain results will have an impact on the ability of a clinic to take on new patients.

Managing uncertainty well will also be relevant to the environmental footprint of genomics, as well as health system stability and sustainability. Providing uncertain information is, as discussed, resource intensive. So too is generating, processing and storing relevant data so that it can be re-examined if or when the underlying science is clearer (Samuel and Lucassen, 2022). To this end, considering uncertainty with a sustainability lens can provide one reason to potentially limit the scope of genomic testing to information that is better characterised. It will also direct care to where it is most needed.

Ultimately, actively appraising uncertainty as part of the processes involved in genetic and genomic testing (especially genetic counselling) will assist in supporting patients. This should include relevant elements of Han *et al.'s* taxonomy, especially those elements of uncertainty that have an ethical dimension. But beyond understanding the various aspects of uncertainty, it is critical that medical providers focus on the therapeutic alliance with patients (Werner-Lin *et al.,* 2016). As Kohut *et al.* (2019) claim: 'A solid grounding in counselling skills and ethics allows genetic counsellors to adeptly manage expectations and complex uncertainty for patients, colleagues and the public and aid decision-making and family communication.' Under this approach, patients - who can struggle with uncertainty (Wöhlke *et al.,* 2019) - will feel better supported to make autonomous decisions, reflecting their own values and circumstances. Some practical suggestions for appraising uncertainty are provided in Table 1. See also: Genetic Counselling; Bioethics of Genetic and Genomic Testing.

Conclusion

Uncertainty is inherent to genomic medicine and to genetic counselling, and will likely remain so in at least the near to medium term. While uncertainty can be a source of hope and optimism, it can also be burdensome and may generate fears, lead to avoidance of decisions or negatively impact well-being (Han *et al.,* 2017). Rather than attempting to dismiss uncertainty or assume that testing will remove it, good practice in genomic health will involve recognising and planning for uncertainty of outcomes, at all stages of the testing process. This will include incorporating uncertainty into counselling and actively pre-empting the ethical dimensions of uncertainty.

Providing genomic medical care in an ethical manner necessitates that we plan for uncertainty, whether it manifests in a positive, negative or neutral manner. Such planning will minimise the negative impact of uncertainty on patients, professionals and the health system. By embracing both the challenges and opportunities of uncertainty, genetic health professionals can provide better care and support to their patients.

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Glossary

Expression, genetic: Process in which information encoded in DNA is used to produce a product (e.g., a protein). First, the DNA sequence is read ('transcription'), and second this information is 'translated' to make the product.

Exome: The coding regions of the genome. In other words, the part of the genome where the DNA is read to start the process to produce proteins.

Genomic sequencing: A laboratory method used to determine a DNA sequence. Most sequencing now uses 'next-generation' methods, which can sequence multiple sequences at once. Sequencing can seek to determine the whole of a person's genome, or certain parts.

Genotype: In the context of genetic testing, a 'genotype' is the DNA base pairs a person has at a certain location in their genome. The identified base pairs may be a 'normal' variant, 'pathogenic' (disease causing) or uncertain.

Penetrance: A measure to denote how often a pathogenic variant causes an effect or symptoms in those who have it.

Phenotype: The observed traits or characteristics of an individual.

Uncertainty: A state of having limited knowledge where it is impossible to exactly describe the existing state or future outcome of a situation.

Variant: A change in the DNA sequence of a gene. A variant can be beneficial, harmful or have no or unknown effect. They can be present from birth, or arise during a person's lifetime.

Variant of uncertain significance (VUS): A change in a person's genome, identified through a genetic or genomic test, where the health impact is not certain. A VUS may be re-classified in the future as either pathogenic (disease-causing) or benign.

Figure 1: A high-level taxonomy of Uncertainty, adapted from Han *et al.* (2017).

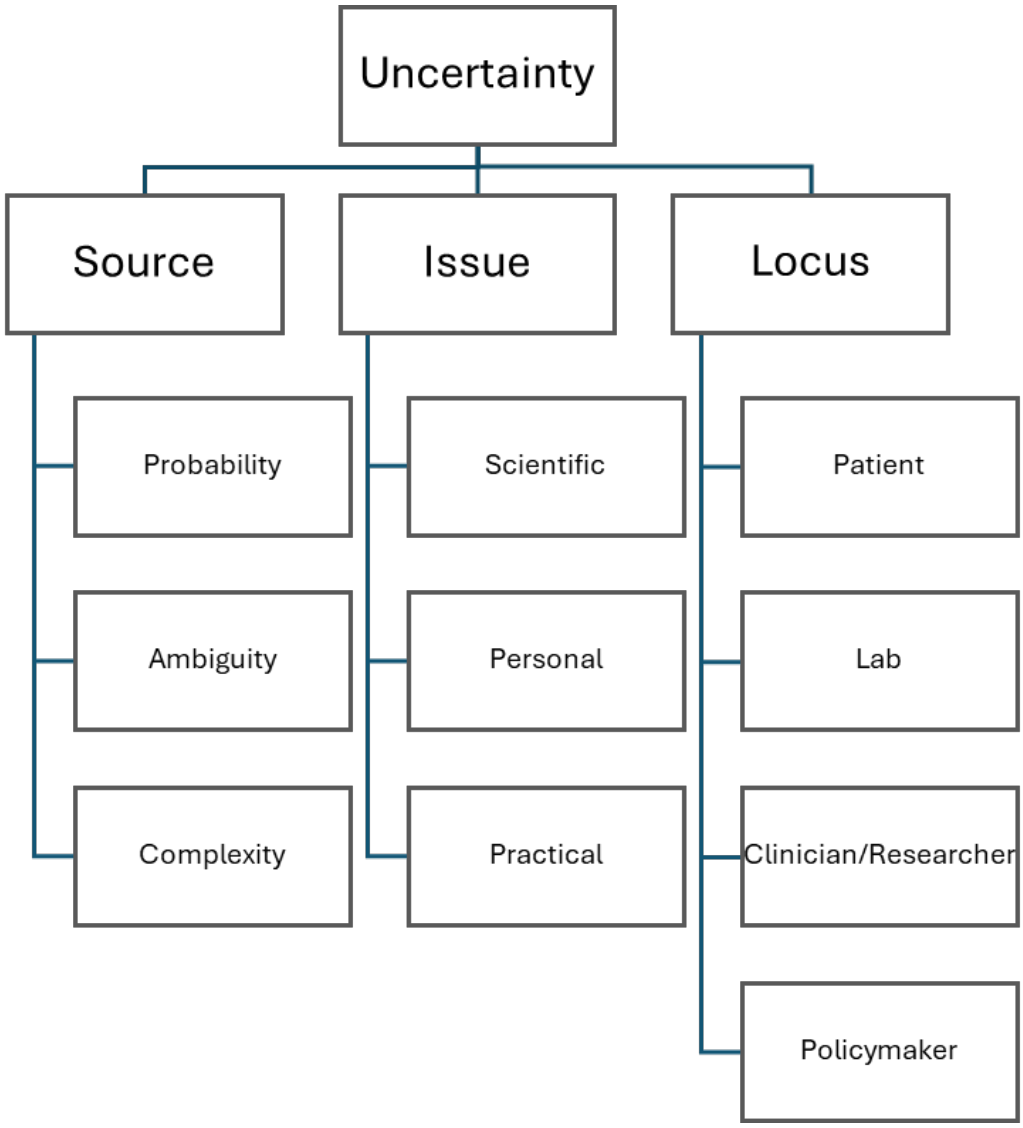

Table 1: Points for practice when appraising uncertainty in genetic and genomic testing

- Uncertainty is embedded in genomics and in precision medicine more broadly (Lohse, 2023). A test in these contexts should not be offered or accepted with the sole aim of reducing uncertainty.
- Build in considerations of uncertainty from the outset of the testing process. Uncertainties can relate to several aspects, including: diagnosis, prognosis and progression, or recurrence.(Barlow-Stewart, 2018; Newson *et al.,* 2016)
- Be transparent about uncertainty, address it during the consent process and aim to manage patient expectations (Jamal *et al.,* 2020) Actively consider uncertainty's empirical (non-normative) and ethical (normative) elements (van der Schoot *et al.,* 2024)
- Tailor support for patients to factors such as their tolerance of uncertainty or ambiguity (Barlow-Stewart, 2018). If uncertainty persists, ensure patients have access to ongoing support (Neustadt *et al.,* 2020). Consider using scales such as PUGS (Biesecker *et al.,* 2017)
- Communicate regularly with patients about uncertainty during the testing process, and encourage effective communication among their family members too (Bradbury *et al.,* 2016; Campbell-Salome & Barbour, 2022; Kuiper *et al.,* 2023; Makhnoon *et al.,* 2019). Counselling strategies like offering a "not yet" diagnosis, with the aim to maintain hope, may be useful (Kuiper *et al.,* 2023).
- With increasing mainstreaming of genetic and genomic testing, recognise when genetic counselling may be indicated. Genetic counsellors play an important role in navigating uncertainty (Hammond *et al.,* 2021; Harding *et al.,* 2020).

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