

## The Certainty of Uncertainty in Genomic Medicine: Managing the Challenge

**Kristine Barlow-Stewart\***

Northern Clinical School, Kolling Institute, The University of Sydney, Australia

### Abstract

While uncertainty has long been a hallmark of the practice of medicine, the need for attention to its management is gaining focus with the movement of genomic testing from the specialist genetics service into mainstream health care. Uncertainty management first requires an understanding of all of the dimensions of uncertainty including recognition of the sources (probability or risk, ambiguity and complexity), the issues (scientific, personal and practical) and the loci (patients/family/research participants, laboratory personnel, clinicians, research investigators and policy makers). At the same time, it is also important to recognise that uncertainty is not always problematic, and therefore needs to be avoided or eradicated or that its psychological impact is necessarily negative. This means that management strategies that foster resilience, welfare, autonomy and solidarity when offering genomic testing may assist in ensuring those receiving and offering genomic health care are prepared for the inevitable uncertainties generated and present results with positive framing. The genetic counseling interventions currently proposed as management strategies are underpinned by, first, pre-test counseling that addresses potential uncertainty as part of the informed consent process. Secondly, a care relationship developed at result delivery fosters trust. This may assist in continued engagement and re-contact with services to facilitate possible future resolution of the interpretation of the genomic result. Nevertheless, it is essential that any intervention is evaluated so that it can be promoted with assurance of rigor.

**Keywords:** Genomic medicine; Variants of uncertain significance uncertainty; Taxonomy of uncertainty; Ethics; Genetic counseling interventions

### \*Corresponding author:

Kristine Barlow-Stewart

✉ kristine.barlowstewart@sydney.edu.au

Associate Professor, Director Master of Genetic Counseling Program, Northern Clinical School, Kolling Institute, The University of Sydney, Australia.

**Tel:** +61 2 9926 4553

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### Introduction

The issue of uncertainty in medicine has always been inherent: from when a patient presents with clinical symptoms that have a variety of possible causes to the unclear prognosis of a diagnosed disease. Han et al. [1] defines uncertainty as the personal perception of ignorance, in contrast to the state of being ignorant. This state has been described as “not knowing what one does not know” [1,2]. Indeed, it is an issue with which many doctors in training have long struggled [1] and since the 1950’s it has been acknowledged that strategies need to be developed to address uncertainty [3].

Developments in technology are increasing accessibility and implementation of genetic/genomic testing across the delivery of healthcare. These developments have however brought focus to

the need to understand and address uncertainty in both patients and providers [4,5].

### Genetic Testing to Genomic Medicine

The Human Genome Project that facilitated testing of known single genes associated with specific conditions heralded the first wave of providing certainty to patients suspected of having a genetic condition or identifying those at risk where there was a family history [3,6]. Yet even when a person was identified with a mutation that rendered them certain to develop a condition in later life, such as Huntington disease, uncertainty was engendered in terms of when symptoms would actually onset [5]. More personal and familial uncertainty is engendered when the result confers not certainty but risk such as with the identification of an inherited BRCA mutation for hereditary breast and ovarian

cancer [7]. Similarly, a certain diagnosis of cystic fibrosis based on the identification of the mutated CFTR gene following Newborn Screening shortly after birth in a baby with no current symptoms creates huge uncertainty about the baby's disease progression given the variable expressivity of the condition [5,6]. Genetic testing is now being conducted using panels of genes, examining all the protein coding genes (the exome) or the whole genome [3,7]. Even when just examining the exome, which constitutes only about 1.2% of the genome, it is suggested that about 20,000 variants in every tested person will be generated [8-10]. Further this genomic testing is moving out of the provenance of the specialist genetics service to mainstream medicine [11]. Such testing is promoted as "precision medicine", implying certainty [12]. However, this increased scale of testing, and these testing methods, in fact add to the uncertainty generated as described above [12].

The interpretation of DNA variants identified on genomic testing relies on multiple lines of evidence. They are then categorised according to the recommendations of the American College of Medical Genetics and Genomics from benign to pathogenic with variants of uncertain significance (VUS) in the middle [13,14]. Uncertainty is embedded when results of VUS are returned but also when there are unexpected findings of pathogenic variants in genes associated with conditions unrelated to that for which testing was conducted (incidental findings - IFs) [5]. The uncertainty is compounded by the changing categorisation of variants with upgrading from uncertain to pathogenic and downgrading to benign as more evidence is accumulated and incorporated in the interpretation [15].

## The Dimensions of Uncertainty

In order to address this genomic uncertainty, it is important to understand its dimensions. In patients with chronic illness, Mishel (1990) [16] described four dimensions of uncertainty: ambiguity, complexity, deficiency of information and unpredictability. Babrow and Kline (1998) [17] expanded on this taxonomy in the broader health care setting, proposing five dimensions: complexity, information quality, probability, the integration of information provided and lay explanatory models for disease causation. Han et al. [1] contested that the focus of these taxonomy on the uncertainty experienced by patients in the era of genomic medicine requires the consideration of other factors contributing to uncertainty including the many types such as scientific uncertainty, their sources and manifestations.

A taxonomy of medical uncertainties generated by clinical genome sequencing was therefore developed in 2017 [18], presented on three axes- source, issue and locus- with further discrimination of the uncertainties engendered into five layers with multiple domains. Three principal *sources* of uncertainty were identified as: (a) probability or risk (associated with uncertain future outcomes); (b) ambiguity (associated with lack of reliable or definitive risk estimations provided and impacted by methodological and clinical issues); and (c) complexity (associated with multiplicity of causes and effects and the presence of modifying factors). The *issues* generating uncertainty in genomic medicine encompassed three dimensions: scientific (diagnostic, prognostic, causal and

therapeutic factors), personal (psychological, social, economic and existential impacts) and practical (structural and procedural factors). Finally, the *loci* of genomic uncertainty included patients/family/research participants, laboratory personnel, clinicians, research investigators and policy makers.

Newson et al. [19] acknowledged that this conceptualisation of uncertainty is essential in informing strategies for response and management by health care professionals in the genomic era. They proposed however that it is also important to recognise uncertainty is not always problematic which needs to be avoided or eradicated as suggested in the past [17] or that its psychological impact is necessarily negative [20]. Building on ethical concepts, they suggest that fostering resilience, welfare, autonomy and solidarity when offering genomic testing may assist in ensuring those receiving and offering genomic health care are prepared for the inevitable uncertainties generated with positive framing [19].

## Genomic Uncertainty Management

Those attending genetic counseling are often motivated to gain information to make sense of the condition in their family but are often met with uncertainty in terms of an inconclusive diagnosis, the chance of an occurrence or recurrence given as an estimate or range and ambiguity about the disease progression or severity [21]. The Need for Cognitive Closure model for example may assist in understanding the motivation of those seeking genetic counseling and how they might manage uncertainty [22]. This model incorporates personal preferences for order and predictability, and discomfort with ambiguity, decisiveness and closed-mindedness.

A number of strategies have been proposed to assist in this management that take into account the taxonomy proposed by Han et al. [18] within the ethical framework proposed by Newson et al. [19]. These strategies are informed by uncertainty management theory which is underpinned by the view that a person's appraisal and emotional response determines how they manage the uncertainty generated: reduction, maintenance, increase or adaptation [23].

## The importance of pre-test counseling

It is essential to address the potential for uncertain results to be generated prior to the test being performed. This needs to be part of the consent process and the discussion can reveal the possible responses that might occur. Biesecker et al. [2] identified that the genomic research participants' responses were predicted by their prior views about genomic information. Those who perceived uncertainty would likely be generated from testing viewed this uncertainty positively and an opportunity for further research. On the other hand, those who did not expect uncertainty or were more averse to ambiguity were more pessimistic about the future use of the technology and perceived it negatively. While the suggestion then for preparation for the results appears sound, the time needed for this will be a challenge as genomic medicine moves to the mainstream. Lazaridis et al. [23] provide some insights into how these challenges may be managed to enable the optimal translation of genomic medicine into wider clinical practice [24].

In the preparation for the potential uncertainty, clinicians need to explore the impact that such uncertainty may have on a patient or their family. It cannot be assumed that a patient prefers certainty: for example, some may prefer not to know they will develop or are at risk for a genetic condition [23]. It is important to also explore views within their family as some members may be more tolerant of uncertainty than others.

Another strategy for preparation is the use of scenario planning [25]. Healthcare practitioners can explore how a patient might feel or what they view life will be after each possible outcome from the testing. This may also raise awareness of potential patient expectations, either conscious or unconscious, of the testing outcomes.

### The care relationship underpinning delivery of an uncertain result

The locus of concern regarding uncertainty by clinicians and researchers is currently focussed on the generation of VUS and IFs and how to communicate the result and manage their impact [11,26]. Stivers and Tinnermans (2016) [27] explored this communication in 44 video-recorded consultations of families who had undergone exome sequencing. Where a result was uncertain, they showed that despite reporting a result documented in a detailed laboratory report, the report was simply a point of reference for the clinicians who engaged with the parents empathetically, ensuring that their explanatory models were addressed. In the process of providing the parents with their reasoning for the result interpretation, allowing parents to question or challenge this reasoning, and providing evidence of what is known to date that informs the interpretation, the clinicians worked together with the parents to appraise the result. This process builds on the concept of solidarity referred to by Newson et al. [19], facilitating the partnership between those offering and providing the testing.

Skinner et al. [28] also noted that uncertain diagnostic genomic

test results congruent with the clinician's interpretation can be relayed to patients without causing harm when the relationship between clinician and patient has facilitated the communication. This trust relationship [29] fostered in this way can influence the next chapter in the variant interpretation whereby the categorisation is upgraded from VUS to pathogenic or downgraded to benign. A challenge for genetics services is how this changed information is provided and most services currently rely on parents and patients to recontact the service to initiate a result re-analysis [5]. If the parents/patients feel they are part of the team working towards diagnostic certainty, it may assist in the fostering of the resilience they require as they deal with the uncertainty in the information they received. Dean and Davidson (2018) [30] also found that when patients receive results for hereditary breast and ovarian cancer predisposition (called "previvors") from clinicians who are knowledgeable, provide information, answer questions, check understanding and provide additional resources, the management of the uncertainty in regard to their cancer development generated is assisted. They propose that this communication strategy distinguished options and fostered meaning for previvors [31].

### Conclusion

While some strategies have already been identified that address uncertainty in the genomic era, with the "mainstreaming" of genomic medicine it is also important that these genetic counseling interventions, and those still to be developed are evaluated. The USA National Society of Genetic Counselors (NSGC) has recently published standards comprising 23 items over eight domains that should be addressed when reporting interventions "to promote synthesis and translation of research and other findings into genetic counseling practice". It is only with this rigor that such interventions will be implemented with confidence.

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