Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, reach and timeliness of genomic research projects, and to support Commonwealth State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy and action for integrating genomic technologies into the health system. By interfacing with consumers, governments, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Evidence brief: terminology for genomic findings beyond the scope of the original test request

There has been considerable diversity in the use of terminology to describe genomic results that are not related to the indication for testing but are considered of medical value or utility. These types of findings may be unintentionally discovered during the course of analysis or intentionally sought.

A debate in terminology arose in part due to confusion after the release of the first "ACMG list" in 2013, which described a list of genes as 'incidental findings' that should be routinely analysed as part of a clinical genomic sequencing test. The term associated with this list was later updated to 'secondary findings' because it was argued by other stakeholders that 'incidental' is not a term that implies a deliberate search for genetic variants[1]. Another issue raised in the bioethics literature is that terms 'incidental' and 'secondary' suggest that a genetic result identified by these means is of lesser importance to the original test results, which is not necessarily the case.

As a result, several other terms have been suggested in both (normative) ethical scholarship and empirical research, and applied to policy in various countries globally. Those terms include, but are not limited to: unsolicited, unexpected, unanticipated, and additional findings. This has resulted in little consistency and ongoing misunderstandings about the types of genomic results being referred to when each term is used. In Australia, there is very little consistency in the terminology used (nor in practices and policy relating to the return of such findings), as evidenced by the results of two surveys involving NATA accredited diagnostic laboratories performing WGS/WES/panel tests (Tudini et al., in preparation). NSW Health Pathology has recently developed a policy on Incidental Findings for Genomics. It defines an incidental finding as one of "medical significance that is present in the genomic data but is unrelated to the reason for referral", but also states that the policy encompasses whether the finding is "systematically searched for or not". It is our view that using one term to cover both unintentionally and intentionally sought genetic findings amplifies the terminology issue as the modes of discovery and process pathways associated with each are distinct.

To work toward harmonisation in Australia with respect to both terminology and guidelines for the return of genomic findings beyond the original indication for testing, Australian Genomics is undertaking a project through the bioethics priority area to develop a set of recommendations for consideration by stakeholders including Australian and jurisdictional governments, professional colleges (e.g. RCPA) and HGSA. This is being done via a two-step approach that will incorporate stakeholder consultation at each step. The first step, development of recommendations about standardising terminology use, is due for completion in early 2022.

Australian Genomics has formed the initial view (subject to consultation) that the term: **'incidental findings' should be used to describe variants in disease-causing genes that are *unintentionally* discovered during the course of analysis, which are not related to the primary indication for testing but which are, on balance, considered to be medically actionable**. This is based on the reviewed evidence:

- Incidental finding is a term used throughout medicine to mean unsolicited or unintentional findings not related to the primary reason for investigation – that is, the term is not unique to genomic sequencing. A commonly cited example is the identification of another pathology through imaging studies (e.g. CT or MRI) performed for a different reason, which reportedly happens in up to one third of cases[2].
- The ACMG initially released their 2013 recommendations[3] to include the intentional searching of a specified gene list with any clinical sequencing test, terming the set of findings from this intentional search 'incidental findings'. ACMG quickly moved away from use of the term incidental with an update to the policy, replacing it with the term 'secondary findings' to refer to intentional searching of their gene list[4], in response to the recommendations put forward by the Presidential Commission on Bioethical Issues[1].
- The MSAC response to the genetic testing for childhood syndromes 1476 application describes incidental findings: "In the genomic context, incidental findings are *unexpected* genetic test results unrelated to the indication for testing."
- The Canadian College of Medical Genetics uses the term incidental findings[5] to define findings outside of the scope of the indication for testing. In contrast, the European Society for Human Genetics has adopted the term unsolicited findings[6] in its policy document. Australian Genomics will include in its consultation whether the term unsolicited would be endorsed by Australian stakeholders.
- Incidental finding is the term that has gained the most traction in clinical sequencing and research settings to describe this kind of finding. In a review of the academic literature undertaken by Australian Genomics, 78 out of 168 publications relating to the field addressed terminology and definitions. 35% of these papers used the term 'incidental findings'. 1% of publications used terms 'unsolicited' or 'additional' findings.

Relatedly, the Australian Genomics working group has formed an initial view (subject to consultation) that **'additional findings' should be the term used to describe genomic results that are *intentionally* sought and which are on balance considered to be medically actionable, but which are not related to the original indication for testing.**

The equivalent term to 'additional findings' that is routinely used, particularly by ACMG in the US, is 'secondary findings'. The term 'additional findings' has been specifically used in Australian studies where families having genomic testing for a genetic condition are being offered the opportunity to receive adult and paediatric findings and/or carrier screening results after the original test[7]. The term has also been adopted by Genomics England in the 100,000 genomes project. Research on participant preferences indicates that 'additional findings' is the preferred term among health consumers to describe this type of genetic findings[8].

Once the review of literature been completed the Australian Genomics working group will broadly consult stakeholders including RCPA, NPAAC, HGSA, Commonwealth and State/Territory Government Department of Health representatives and the Australian Genomics network (namely through the Clinical, Diagnostic and Research and Policy Networks, as well as the Community Advisory Group) on their views before formalising recommendations on terminology use.

Australian Genomics welcomes the opportunity to discuss with the NPAAC Guidelines drafting committee during updating "Requirements for medical testing for human genetic variation" to determine the adoption of terminology and guidelines that are most appropriate and supported by stakeholders in relation to the feedback of genomic sequencing findings to patients.

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