

Incidental findings in clinical research: the case of the 'known unknowns'

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The practical implications of developing a standardized set of obligations for the research community to adhere to, in the management of current and future incidental findings (IFs), is a staggering exercise to contemplate. Consider the growing use of research biobanks (which is a repository of biological samples), the evolving field of genomic research, and the potential of patients seeking subsequent care based on an incidental clinical research finding could lead to significant additional time and resources to an already burdened enterprise [1]. Although maintaining the public's trust in research remains vital; the stakes involved in how IFs are to be managed are quite high for participants, researchers and the health system.

In academia, seeking out common language and terminology are crucial to fostering productive dialogue in the exploration of any issue. However, the literature on IF continues to make reference to an unwieldy array of terms: abnormal, incidental, accidental, secondary, significant, unexpected, unrelated, unforeseen, unusual and variant, are some of the potential adjectives that have been used to precede the word 'finding' [2].

For the purposes of this editorial, I will apply a classic definition to explicate the concept of IF as it relates to clinical research: IF is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study [3]. For example, envision a medical imaging researcher that is examining structural attributes of the frontal cortex in healthy volunteers and in the course

of research discovers that a participant has a glioblastoma, which is a brain tumor.

In its earliest consideration, IFs were considered to be so rare and uncommon that researchers merely considered their discovery as being something that was stumbled upon in the moment and they had no idea whether or not to share this information with research participants. This phenomenon became affectionately called the 'stumble strategy' [4] and remained the status quo until the past decade.

However, the following small sampling of recently reported occurrences of IF in clinical care tell another story:

- Chest computed tomography to diagnose pulmonary embolism generated IFs that outnumbered intended findings by 2:1 [4];
- Clinically significant noncardiac findings are commonly encountered in 5% of patients undergoing a cardiac MRI (patients 60 years old and older are approximately 12-times more likely to have a significant noncardiac findings than younger subjects) [5];
- In the USA and Canada, the prevalence of father-child living kidney donor–recipient pairs with misattributed paternity is between 1 and 3% [6];
- Currently, it is estimated that 2.2% of adults can be expected to have actionable highly penetrant pathogenic mutations identified by exome sequencing [7].

Based on these illustrative findings, the long-standing notion of a finding being



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somehow ‘incidental’ can and perhaps should be called into question given that they are increasingly foreseeable. This growing prevalence of IFs also represents a blurring of the line that once safely divided clinical care from research [8].

If we apply Donald Rumsfeld’s infamous taxonomy of ‘known unknowns’ [9] to our evolving perception surrounding the occurrence of IF in clinical research we can come to consider them more as ‘known unknowns’, rather than the ‘unknown unknowns’ categorization previously used to explain their existence in the discovery process.

“Ethical concerns related to paternalism and the bounds of autonomy continue to play out in the context of incidental findings and the public.”

In 2013, the Presidential Commission for the Study of Bioethical Issues published its much awaited report: “Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts” [10]. This report attempts to inculcate the principle of beneficence, imbedded in the Common Rule, by calling on researchers to look beyond the traditional primary goals of research as the basis for their interaction with research participants [11]. The report outlined a set of cascading duties for researchers: to anticipate what might come up in the testing undertaken; to create a plan for how this information might be communicated to the research participant; and to inform research participants of the likelihood that a particular test or procedure will yield an incidental finding. To this end, the Commission outlined a need for the Investigators to work closely with ethics review boards in the development of this ‘anticipate and communicate plan’ as part of the study protocol.

The commission report presented a framework for working with IFs that brought into consideration the following features into the management of findings: the analytic validity of the test; the clinical validity and certainty of the causal mechanism; the clinical actionability available to work with the finding; the clinical or reproductive significance; and the magnitude of the potential harm existent from the finding [10]. Once a decision is reached, the challenge of deciding how the information should be conveyed requires special consideration in light of the special nature of genetic information and its implications, such as counseling needs and follow-up support may require that genetic counselors be a part of the process [11].

Laudable as the commission’s recommendations may be, the lack of scientific and clinical consensus on which results meet the requisite threshold for each of

the above five criteria remains a point of contention over the Commission’s report [9].

In addition to the threshold ambiguity, some in the bioethics community are advocating for an enhanced duty to anticipate and disclose findings. This would involve a duty to actually seek out potential secondary findings particularly when the research protocol involves whole genome sequencing. Though this proposal is actively being debated, it currently remains at the fringes of ethical consideration. However, the advancement of genomic medicine and the potential for these results to favor preventative healthcare will undoubtedly keep this idea of obligation present. The contested border between clinical care and clinical research continues to be eroded and new duties of the type proposed will push researchers to act more as clinicians in their search for generalizable data [11].

Given what I have been discussing to this point, it may be helpful to refocus our conversation on the duties and obligations of researchers relating to ensuring that research can continue to be accountable to the public via trust. One could argue that ‘trust’ is a core ethical value at stake in this issue and that moving forward in the scientific pursuit of truth we must carry with us the trust of the public to which we are beholden [11].

Empirical research on the public’s perspective toward IFs lags behind the evolving scientific evidence that places these findings in a clinically relevant realm. Issues of ownership of the IFs aside, in order to proceed judiciously and ethically, we need to better understand a person’s reaction to IFs and to conduct research on how best to inform and educate participants so they can make better informed choices about whether to participate in research that may involve an IF [11]. However, this only represents one side of the equation. The research community must provide a consistent approach to investigate ways to manage IFs when they arise and this approach must take into consideration the inevitability that IFs may involve an increased need for medical care in order to properly address these issues.

Ethical concerns related to paternalism and the bounds of autonomy continue to play out in the context of IFs and the public [2]. A decision to restrict the type of information to be disclosed in IF based on any fair minded criteria (such as actionability for the IF) can appear paternalistic given that IFs have impact beyond the clinical domain (e.g., reproductive and psycho-social concerns). Similarly, the principle of autonomy and the right of research participants to opt out comes under scrutiny when it is known that a distinct subset of genes and variants could be acted upon and have a significant potential to prevent disease,

decrease mortality and morbidity, if addressed in the presymptomatic phase [12].

Attempts to address these issues are complicated by the ever changing shift of roles that scientific discovery affords: from that of the bystander when dealing with unknown unknowns to that of health advocate when dealing with known unknowns [13].

In the past, a pure researcher was granted allowance to encounter measured harms when they were carefully balanced against their potential benefits such as the advances of successfully treating harmful biological states. The impact of IFs and an evolving understanding of them, catapults researchers into a

unique situation that transcends the research domain. Regrettably, this bell can never be ‘un-rung’.

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