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Revealing the Incidentalome When Targeting the Tumor Genome

Yvonne Bombard, PhD^{1,2,3,+}, Mark Robson, MD^{1,5}, and Kenneth Offit, MD, MPH^{1,4,5,6,*}

¹Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center

²Center for Health Policy and Outcomes, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center

³School of Public Health, Department of Epidemiology and Public Health, Yale University

⁴Cancer Biology and Genetics Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

⁵Department of Medicine, Weill Cornell Medical College

⁶Department of Public Health, Weill Cornell Medical College

Personalized (or precision) medicine promises to use genomic information to improve the prevention, diagnosis and treatment of disease. This promise is particularly anticipated in the arena of cancer treatment. Academic cancer centers and commercial laboratories are rapidly developing programs to routinely analyze individual cancer genomes to identify therapeutic targets and individualize care.¹ However, the process of decoding the genome of a patient's tumor may incidentally reveal information about inherited predispositions to cancer and other diseases (the “*incidentalome*”). There is an urgent need to establish approaches to decision-making with respect to the return of these incidental results.

Most of the DNA sequence of a patient's tumor is identical to the DNA sequence of the normal cells of that patient (germ-line sequence). For this reason, the process of defining the potentially targetable mutations that are driving a cancer requires the delineation and “subtraction” of germ-line sequence from tumor sequence so as to identify those variations that are specific to the cancer. Incidental information can be found indirectly (when meaningful germ-line mutations are identified in the tumor sequence), or directly (in the normal DNA that is sequenced for comparison to the tumor DNA). As an example, sequencing a tumor/normal pair of samples from a lung cancer patient may reveal both an *EGFR* mutation to target with a specific anticancer drug (e.g. gefitinib and the incidental finding of a mutation in *RYR1* that would predispose to malignant hyperthermia upon exposure to certain anesthetic agents. In many cases, however, the medical significance of incidental germ-line findings may be unclear. A vigorous ethical debate has unfolded regarding whether laboratories and clinicians have an obligation to inform patients about

*Correspondence: Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, 222 E 70th Street, New York, NY 10021, t: 646.888.4059 | f: 646.888.4081.

+current address: University of Toronto, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario M5B 1W8, Canada

contributions

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certain incidental findings, or if such an obligation would constitute a violation of a patient's autonomous right to decide what genetic information he or she wishes to learn.²⁻⁴ While most of the illustrative examples chosen in this debate are drawn from clinical cancer genetics, oncologists have yet to join this discussion³.

Revealing the incidentalome when targeting the tumor genome

Most pipelines for fully characterizing cancer genomes require germ-line DNA sequence as a comparator. Each individual's genome contains ~20,000 sequence variants in protein-coding genes, including variants associated with current (but unrecognized) disease, future disease risks, drug response, carrier status, and variants of uncertain significance. A number of commentators have suggested that "medically actionable" variants should be returned to patients, but there is debate regarding what constitutes a "medically actionable" variant. The American College of Medical Genetics has proposed a list of 58 genes (25 of which pertain to cancer risk), with the recommendation that laboratories report variants in these genes if they are identified in the course of clinical sequencing².

Elaborating the germ-line in tumor sequencing

To determine genomic sequence (tumor or normal), DNA is first fragmented, then amplified, after which the ends of the fragments are read or "sequenced" simultaneously in "massively parallel" fashion. The "reads" are then aligned to a reference genome. Any site in the input DNA that differs from the reference sequence is considered a sequence variant. Variants that are specific to an individual's cancer (and thus potential targets) are defined by subtracting the variants present in the "normal" (germ-line) genome from the variants found in the cancer genome. This comparison is typically performed computationally prior to the generation of the final list of cancer-specific variants, without generating a specific list of sites where the germ-line DNA sequence differs from the reference. Thus, the raw germ-line sequence data alone do not constitute 'results' in any sense that warrants disclosure until the germ-line sequence variants are explicitly enumerated, which requires additional analysis.

At present, tumor sequencing is carried out in two contexts: retrospective research to define the molecular mechanisms of the success or failure of targeted therapies, and prospective research and clinical care. The decision whether to report medically relevant germ-line variants found during tumor genomic profiling has profound ethical and clinical implications, which differ according to context.

Retrospective research context

Forgoing dedicated analysis to identify germ-line sequence variants may be crucial in retrospective research that is conducted on samples for which participants' preferences with respect to incidental results were not defined at the time of ascertainment. It may not be possible to re-consent such individuals to determine these preferences due to their loss from follow-up, death, or other reasons. Removing these samples from analysis may compromise important studies by creating biases, or by preventing utilization of complete sample sets. On the other hand, conducting germ-line testing without individual consent raises ethical issues. Thus, avoiding the explicit definition of germ-line variants at the time of tumor

genetic analysis strikes a balance between the goals of a research study and the ethical protection of patient privacy and autonomy, albeit at the cost of losing predictive genetic information.

Prospective context for research and clinical testing

When the individual being offered genomic testing can be engaged in a discussion of informed consent, whether in a research or clinical context, there is ample opportunity to discuss disclosure of incidental findings. The method of purposefully not enumerating germline variants removes information that may be relevant to medical care. Such incidental genetic information may be relevant to treatment toxicity and effectiveness, and to the disease risks of the patient and his or her family members. Given the increasing interest among patients in accessing their genomic information⁵, and given potential legal obligations to warn individuals of medically actionable information^{6,7}, it will be important to explicitly review in informed consent discussions for prospective research or clinical testing how incidental results will or will not be communicated. In fact, the need for this discussion is a major argument for obtaining informed consent for clinical tumor genomic profiling as well as for research testing.

Barriers to disclosure of incidentally discovered genomic findings

Even if an individual wishes to learn incidental results, there remain significant barriers to disclosure of this information. These barriers include the practical limitations of providing multi-gene genomic counseling, the need for confirmation of research findings in a CLIA-certified laboratory, challenges in determining whether certain inherited variants are truly pathogenic, and the high rate of indeterminate, false-positive, and false-negative results generated by next generation sequencing (NGS)⁸. In addition to the scientific challenges, there is an ethical debate between those arguing that disclosure should be governed by respect for the autonomous right of choice to learn results of incidental findings and those who believe that there is an obligation to disclose all actionable results without explicitly determining patient preferences²⁻⁴. Unfortunately, a globally restrictive position would deny patients the potential benefits of incidental findings while a globally permissive stance ignores the fact that there are some genetic test results that patients do not wish to know (e.g. *p53* germline status in approximately half of those eligible for presymptomatic assessment). The conflict between these opposing viewpoints may be resolvable by new pre-test counseling and consent approaches that would determine the patient's preference for the general types of incidental information he or she would want to receive, without requiring specific decisions about individual genes.⁹ Continued research and input of stakeholders will be required to develop this individualized approach to genomic counseling.³

Conclusions

Optimal interpretation of the cancer genome requires a comparison to the inherited genome, but it is possible to avoid explicit enumeration of inherited variants. This strategy is justifiable in retrospective genomic research, but is less supportable in the prospective setting. For prospective research and clinical translation, the path forward depends on

approaches that better define actionable variants and the development of the evidence base and clinical infrastructure to support preference-based disclosure of incidental findings. This will require the creation and evaluation of decision tools and the clinical capacity to provide genomic counseling, for which no standards of care exist. Understanding how patients and clinicians interpret, manage, and utilize the genomic information they receive is essential to measure health service outcomes, risk-benefit trade-offs, and overall cost-effectiveness.⁸

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References

1. Pasche B, Absher D. Whole-genome sequencing: a step closer to personalized medicine. *JAMA*. 2011 Apr 20; 305(15):1596–1597. [PubMed: 21505140]
2. Green RC, Berg JS, Grody WW, et al. ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. *Genet Med*. 2013; 15:565–574. [PubMed: 23788249]
3. Klitzman R, Appelbaum PS, Chung W. Return of Secondary Genomic Findings vs Patient Autonomy: Implications for Medical Care. *JAMA*. 2013 Jul 24; 310(4):369–370. [PubMed: 23917282]
4. Ross LF, Rothstein MA, Clayton EW. Mandatory Extended Searches in All Genome Sequencing: “Incidental Findings,” Patient Autonomy, and Shared Decision Making. *JAMA*. 2013 Jul 24; 310(4):367–368. [PubMed: 23917281]
5. Bombard Y, Abelson J, Simeonov D, Gauvin FP. Citizens' perspectives on personalized medicine: a qualitative public deliberation study. *Eur J Hum Genet*. 2013 Jan 23. [Epub ahead of print].
6. Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA. The “duty to warn” a patient's family members about hereditary disease risks. *JAMA*. 2004 Sep 22; 292(12):1469–1473. [PubMed: 15383518]
7. Bombard Y, Offit K, Robson ME. Risks to relatives in genomic research: a duty to warn? *Am J Bioeth*. 2012 Oct; 12(10):12–14. [PubMed: 22974020]
8. Bombard Y, Bach PB, Offit K. Translating genomics in cancer care. *Journal of the National Comprehensive Cancer Network (JNCCN)*. In press.
9. Goddard KA, Whitlock EP, Berg JS, Williams MS, Webber EM, Webster JA, Lin JS, Schrader KA, Campos-Outcalt D, Offit K, Feigelson HS, Hollombe C. Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies. *Genet Med*. 2013 Apr 4. [Epub ahead of print] PMID:23558254.