

# Normative and conceptual ELSI research: what it is, and why it's important

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The Ethical, Legal, and Social Implications (ELSI) Research Program of the National Human Genome Research Institute sponsors research examining ethical, legal, and social issues arising in the context of genetics/genomics. The ELSI Program endorses an understanding of research not as the sole province of empirical study, but instead as systematic study or inquiry, of which there are many types and methods. ELSI research employs both empirical and nonempirical methods. Because the latter remain relatively unfamiliar to biomedical and translational scientists, this paper seeks to elucidate the relationship between empirical and nonempirical methods in ELSI research. It pays particular attention to the research questions and methods of normative and conceptual research, which examine questions of value and meaning, respectively. To illustrate

the distinct but interrelated roles of empirical and nonempirical methods in ELSI research, including normative and conceptual research, the paper demonstrates how a range of methods may be employed both to examine the evolution of the concept of incidental findings (including the recent step toward terming them 'secondary findings'), and to address the normative question of how genomic researchers and clinicians should manage incidental such findings.

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## NORMATIVE AND CONCEPTUAL ELSI RESEARCH: WHAT IT IS, AND WHY IT'S IMPORTANT

In 1990, Congress appropriated funds as part of the Human Genome Project to create the Ethical, Legal, and Social Implications (ELSI) Research Program “to foster basic and applied research on the ethical, legal and social implications of genetic and genomic research” (<https://www.genome.gov/elsi/>). The impact of ELSI research is evident in subsequent scientific and public policy, conduct of genomic research, and implementation of genomic medicine,<sup>1</sup> with ELSI research credited, for example, with changing the way investigators draft consent forms for genomic studies, informing policies and governance mechanisms for biobanks/repositories, advancing understanding of how people perceive risk, clarifying the meaning of race in genomic research, and influencing intellectual property law surrounding genomics.

The recognized value of ELSI research has led to increasing calls for ELSI researchers to collaborate with genomics researchers and even to embed ELSI research within genomic research projects.<sup>1</sup> Moreover, partly as a result of the ELSI Program's success, the term “ELSI research” has become familiar and indeed is used beyond the context of both National Human Genome Research Institute (NHGRI) and genomics research to describe ethical, legal, and social

research in other domains, including synthetic biology<sup>2</sup> (e.g.), neuroscience,<sup>3</sup> nanotechnology,<sup>4</sup> Big Data,<sup>5</sup> and other emerging technologies in information and computing science<sup>6</sup> and diagnostics.<sup>7</sup> Despite the prevalence of ELSI research related to genomics (and its increasing presence regarding other fields), the methods employed in some ELSI research—particularly normative and conceptual research—remain relatively unfamiliar, even opaque, particularly to researchers in the basic biomedical and translational sciences.

In this paper, we explain methods of ELSI research with reference to genetics/genomics research, though we believe the explanation may be of value to scientists in many fields. While several recent efforts have sought to explain the methods and value of ELSI research, for example by devising comprehensive taxonomies that include normative and conceptual research and that clarify its relationship to empirical approaches or to policy development (e.g.,<sup>8,9</sup>), we pay particular attention to the nonempirical methods employed to address normative and conceptual questions and to the nature of the questions they address. This paper proceeds from the understanding that “research” is not solely the province of empirical study, but refers more broadly to systematic study or inquiry, of which there are many types and methods. Using as an example the problem of how

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researchers and clinicians should manage incidental findings of genomic testing, we elucidate the range of methods used in ELSI research. In particular, we demonstrate the relationship of conceptual research—here, focused on the evolution of the meaning of ‘incidental findings’ and the introduction of ‘secondary findings’—to normative research, including the method of argument.

### ELSI RESEARCH ON WHAT IS AND WHAT OUGHT TO BE

In the classic divide between what is and what ought to be, science seeks to know what is. Science poses and pursues empirical questions (e.g., is there an association between genetic variants on chromosome 7 and cystic fibrosis?) by observation and by empirical methods (e.g., linkage analysis or genome-wide association studies [GWAS]).

ELSI research involves asking questions on both sides of the classic divide between “is” and “ought.” Some ELSI research asks what the implications of genomic research *are*, and employs empirical research methods to collect data to test hypotheses, evaluate programs, or develop a theory of a phenomenon. Do people receiving genetic test results suffer emotional distress? Does persistence of posttest distress correlate with pretest temperament or traits? The empirical methods used to pursue these ELSI questions are familiar not only to social scientists but to basic biomedical and translational scientists.

However, other questions cannot be addressed solely or primarily by analyzing data, because they ask questions about value and meaning. These value-focused normative questions and meaning-focused conceptual questions require nonempirical research methods, including philosophical and legal analysis (and argument), and the methods of the humanities. Answering questions of value and meaning requires evaluating, among other data, what people think, and then providing reasoned arguments to inform subsequent consideration of the issues, as well as future directions for research.

While scientific research pursues what “is” in terms of observable facts, conceptual research focuses on “is” in the special sense of “what is meant by.” What, for example, is meant by “health,” “race,” or “research”? Of course, one could conduct an empirical study and discover that, for example, 65 of 100 people surveyed think of race as a biological fact, a grouping of people according to shared biological features or physical traits. Conceptual research, however, is not concerned solely with learning what people mean by the concepts they use, but also seeks to understand the origins, variety, and implications of these understandings. Conceptual research frequently offers, and perhaps argues for, alternative conceptualizations. Conceptual research on race may, for example, examine the origins of the concept and argue that use of “racial categories” in other research should not be separated from the genealogy or history of the concept (e.g.,<sup>10</sup>), or argue that race is a socially constructed concept and should not be reified (e.g.,<sup>11,12</sup>). Conceptual research may

examine the implications, for example, of viewing and using race as a “sorting schema.”<sup>13</sup>

Further, in contrast to science’s focus on discovering what “is,” normative research is concerned with “ought” or with what action (or policy or practice) is ethically justified or most appropriate. If a study reveals an incidental finding (e.g., misattributed parentage), should an investigator reveal that finding? If so, to whom? Should the informed consent process specify whether incidental findings will be revealed? If an incidental finding has health implications for other family members, should the law permit or compel a clinician to attempt to inform those family members, perhaps over the objection of the patient tested? Data—about family members’ preferences, different cultural views (for example, regarding paternity), the terms of the informed consent document, studies of psychosocial responses to return of incidental findings, and existing laws—are relevant to addressing these normative questions, because they may help to *inform* the analysis. However, these facts alone cannot answer questions of what should be done or what a policy or law should be.

### ARGUMENT: A METHOD OF NORMATIVE RESEARCH

Normative research seeks to discover, and inform or persuade people, what they ought to do, according to some set of norms or values. These may include ethical, legal, religious, and cultural values. Just as scientific theories may be evaluated and compared in light of desirable features such as their internal consistency, simplicity, explanatory power, and “fit” with other theories,<sup>14</sup> normative research may examine different arguments and sets of values to assess consistency, utility, scope, and fit with other value commitments.

To scientists—or to those steeped in what they understand to be a largely value-free scientific tradition that seeks the truth with an open mind—a research method involving making arguments in support of a claim may appear spurious. Unlike scientists who must not assume what they seek to prove, researchers engaged in normative argument appear to begin with their conclusion. In ethical (and many legal) arguments, this is a value-laden claim (e.g., that X is right, that Y is justified, that Z is fair or beneficial, that people’s preferences are the most important consideration, or that the expectations established during informed consent must be fulfilled). Then normative researchers seek ways of reasoning, as well as empirical evidence, that support that claim.

The most methodologically sound arguments consider counterarguments and do not simply ignore contrary normative claims. Instead they attempt to refute them, perhaps by showing that they embrace inconsistencies, lead to untenable conclusions, or support undesirable practical consequences. They also do not simply ignore empirical evidence that seems not to support the conclusion, but instead explain why that evidence is flawed, not really relevant, misinterpreted, or ambiguous. Responding to counterarguments and contrary evidence in this way can

maintain and even strengthen support for the original claim or conclusion.

Both scientific and normative claims are falsifiable, but differently falsifiable. Sometimes the investigator making a normative argument discovers that her initial claim cannot be upheld. She discovers that her argument cannot really be made—or is not as strong—as she anticipated. Perhaps she was partly or completely wrong about the empirical facts or the relationship of ideas, or overlooked some considerations (empirical or normative). Perhaps the argument proved to be contradictory. She may then modify her claim/conclusion, perhaps making it more modest or adding some qualifications or constraints to her position. Or, she may abandon her original conclusion/claim, and pursue another line of reasoning. Just as an hypothesis may not be supported or may be disproved, a normative claim can fail to be supported or be ultimately unsupportable or untenable. Just as in science, such a refutation or negative finding may still advance basic understanding or suggest new avenues of inquiry or claims to be examined.

In the absence of, or prior to normative ELSI research on a topic, people—scientists, clinicians, the public, and ELSI researchers themselves—may have more or less well-grounded opinions, for example, about which incidental findings should be offered to research participants or patients. Normative research lays out the range of possible opinions, indicates which are more strongly supported than others, and establishes consistency among well-grounded opinions. People, including ELSI researchers, may still disagree about particular issues or frameworks for considering issues, but basic conceptual and normative research advances our understanding and allows the arguments between disagreeing parties and positions to become more clearly focused on remaining points of disagreement while acknowledging common ground. We—both those engaged in ELSI research and those who are the audience for it—move toward ever more nuanced arguments. Along the way, ELSI investigators frequently find points of overlap and areas where compromise of apparently opposing positions can be justified to those on both sides of an argument (e.g.,<sup>15</sup>). Policies and practices supported by strong ethical arguments may be considered the applications of basic normative research, much as basic science is translated into or applied in evidence-based medicine.

Then, another wave of empirical ELSI research may undertake to evaluate these policies and practices—for example, surveying the public's acceptance of a policy implemented regarding the return of incidental findings of various types, or studying the psychosocial response to the return of such findings. In an iterative process, these empirical findings can then be used to inform future normative analyses, which in turn are used to shape future policies and practices.

Using as an example the question of how genomic researchers and clinicians should manage incidental findings, we illustrate the distinct but interrelated roles in ELSI research of empirical and nonempirical methods, including normative and conceptual research.

## ELSI RESEARCH REGARDING THE MANAGEMENT OF GENOMIC INCIDENTAL FINDINGS

Prior to and during the Human Genome Project, incidental findings in genetics were often conceptualized as unanticipated or unexpected findings.<sup>16</sup> Misattributed paternity discovered by clinicians in the course of carrier testing or by researchers in family studies, as well as a growing understanding (and number of cases) of pleiotropy, were the most frequently noted examples.<sup>17</sup> Indeed, such findings were discovered with sufficient frequency that they were far from unexpected in the field, even if they were unexpected/unanticipated on the part of particular individuals and families. As management of incidental findings of genomic research became a more pressing concern, the need emerged for conceptual analysis about the very concept of “incidental findings,” a term that was borrowed from diagnostic and research uses of imaging technologies.<sup>18</sup> Could they be conceptualized as unanticipated or unexpected findings if investigators and clinicians were being urged to plan for their discovery? Conceptual analysis suggested that explaining them as “a finding concerning an individual research participant that has potential health or reproductive significance and is discovered in the course of conducting research but is beyond the aims of the study”<sup>19</sup> was more helpful to the normative project of recommending that investigators plan for their management.

With increasing recognition that genomic technologies—especially genome or exome sequencing—give rise to incidental findings, it became clear that investigators and clinicians needed to plan to manage these findings, i.e., to decide whether and which findings to disclose to research participants and patients, and how to disclose them.<sup>20</sup> These normative questions about what *ought* to be done cannot be addressed by empirical data alone; assessing people's preferences regarding return of incidental findings, for example, cannot answer the question of whether the findings *should* be returned or under what conditions. Although data about people's preferences are relevant to drafting policies about return of incidental findings, the normative policy question (the “ought”) must also be informed by normative (value-based) analysis of why and how much preferences should matter for policy.<sup>2</sup> Moreover, given people's differing preferences, a normative position must be taken on whose preferences should matter or matter most. Which stakeholders' preferences should be given most weight: those whose samples actually yield incidental findings, all those involved in the study who might have incidental findings discovered, or professionals (investigators or clinicians)?

More recently, it has been argued that there is an ethical obligation to search intentionally for such findings when performing clinical sequencing for a primary diagnostic question.<sup>21</sup> This normative stance has led to further conceptual analysis criticizing the very idea of an *incidental* finding and supporting reconceptualization of these findings as *secondary* findings: findings of “a deliberate search for pathogenic or likely pathogenic alterations in genes that are

not apparently relevant to a diagnostic indication for which the sequencing test was ordered.”<sup>23</sup> The change is not merely in terminology; it marks a shift in normative stance among some ethicists, genomicists, and clinicians. Even those who disagree—i.e., who do not endorse there being an obligation to search for or offer back such findings—tend to embrace the concept of secondary findings, if only to communicate effectively with those with whom they disagree.

### CONCLUSION

ELSI research employs both empirical and nonempirical research methods. Conceptual research increases conceptual clarity by examining what is meant by various terms and ideas, and arguing that some understandings are better justified than others. Ethical, social, and legal issues—and research on those issues—frequently have conceptual components whose meaning may be contested. Conceptual research may begin by mapping out and comparing possible meanings, but usually makes an argument that there are good reasons to conceptualize something—e.g., race, incidental findings, preferences—in a particular way. Based on reasons specified, something *should be understood* to have a particular meaning or *should be conceptualized* in a particular way.

After a requisite degree of conceptual clarity has been achieved, normative research may map out a range of possible courses of action or reasonable positions to take in regard to a question of value, i.e., a question about what should be valued or what should be done. Normative research then seeks to evaluate these options—usually with the goal of guiding action.

Normative research proceeds by making arguments that are grounded in value commitments, supported by empirical evidence, and assessed in terms of their consistency, utility, scope, and fit with other value commitments and empirical data. Normative research may study, for example, what role people’s preferences should play in determining whether incidental/secondary findings should be offered to participants in genomic research. According to some normative arguments, people’s preferences should be decisive or at least should be given great weight.<sup>22,23</sup> Other arguments are made, however, that people’s preferences are only one consideration among many, such as the economic costs and psychological impact of return, the result’s clinical utility, the impact of return on healthcare utilization, and effects on therapeutic misconception, public understanding of research, and researcher–participant relationships.<sup>23–26</sup> Normative analysis must be invoked to address the normative question of which data should be brought to bear on policy development, and how. While empirical ELSI research can, for example, survey people’s preferences, measure healthcare utilization, and elucidate any constraints imposed by existing law, normative research provides arguments about how to weigh these considerations.

ELSI research employs both empirical and nonempirical research methods. Conceptual research increases conceptual clarity by examining what is meant by various terms and

ideas, and arguing that some understandings are better justified than others. Normative research proceeds by making arguments that are grounded in value commitments, supported by empirical evidence, and assessed in terms of their consistency, utility, scope, and fit with other value commitments and empirical data. Just as scientific research that seeks to discover facts and explain phenomena does not result in “once and for all,” immutable accounts of what “is,” ELSI research yields guidance for action that also evolves as conditions change, new information is discovered, and better arguments are made.<sup>27</sup>

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### DISCLOSURE

The authors declare no conflicts of interest.

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