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Ethics and Collateral Findings in Pragmatic Clinical Trials

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INTRODUCTION

Pragmatic clinical trials (PCTs) are becoming widespread, driven by their promise to generate knowledge more efficiently than traditional explanatory trials and to inform real-world health care decisions (Califf & Platt 2013; Weinfurt et al. 2017). Funding agencies, including the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI), are making substantial investments in both individual trials and research infrastructures to support the future expansion of PCTs (NIH 2013; Hernandez, Fleurence, and Rothman 2015).

PCTs have generated several notable successes. For example, PCTs likely contributed to a significant reduction in deaths from myocardial infarction within United States (US) hospitals and to increasing life expectancy for patients with cystic fibrosis (Califf and Sugarman 2015). However, PCTs may also present ethical challenges (Califf and Sugarman 2015). One such challenge that has not yet been well-described involves what do when PCTs generate information that is unrelated to the primary research question(s), yet may have implications for the individual patients, clinicians, or health care systems from whom or within which research data were collected. For example, a PCT aimed at increasing the uptake of cardiac care guidelines using insurance claims data identified individuals with diagnoses that increase their risk for a cardiac event, but not corresponding documentation that the diagnosis was communicated to the patient, suggesting that a critical opportunity might have been missed to reduce such risk (cite pending). In addition, a PCT exploring strategies to increase colonoscopy screening rates consistent with clinical guidelines unexpectedly revealed that screening tests used by some clinics have far higher positive results than others. This suggested higher rates of false positives among some tests,

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potentially driving unnecessary follow-up testing, and thus creating burdens for patients, clinicians, and health systems (Nielson CM, Petrik AF, Jacob L, et al. 2018).

How should researchers and health systems manage such findings? Prior scholarship of the return of results that may have clinical implications for individuals in explanatory trials and clinical care has examined various ethical issues. In explanatory research, an *incidental finding* (IF) has been defined as a finding that has potential importance for health, reproductive decision-making, or personal utility that is “discovered in the course of conducting research but is beyond the aims of the study” (Wolf 2013). A *secondary finding* (SF) is a finding that is “actively sought by a practitioner that is not the primary target” (Presidential Commission 2013). The chief difference between an IF and a SF hinges on whether generation of the result was intended. Extensive deliberation has supported the development of ethical guidance for the management of IFs/SFs arising in explanatory research and of IFs arising in clinical care (Presidential Commission 2013; Christenhusz, Devriendt, & Diericks 2013). To date, however, such issues have not been addressed in the context of PCTs, which often differ structurally from both explanatory trials and from clinical care—differences that, as described below, are ethically salient, thereby limiting the applicability of existing guidance for PCTs.

In this article, we focus on individual-level findings arising from PCTs (discovered intentionally or unintentionally) that may have implications for health, but which were not generated to address the PCT’s primary research questions. We term these findings as “pragmatic clinical trial collateral findings,” or “PCT-CFs”. We explore the ethical considerations associated with the identification, assessment, and management of PCT-CFs, and how these considerations may vary based upon the attributes of a specific PCT. PCTs may also generate cluster-level collateral findings; however, we will not examine extensively these issues here.

We begin by briefly describing PCTs and their features that create distinctive ethical complexity. Next, to identify ethically relevant features to guide decision-making for PCT-CFs, we explore literature that examines ethical obligations concerning the related issues of IFs and SFs in explanatory research or clinical care and describes settings that are analogous to the PCT context. Our purpose is to map the terrain of PCT-CFs to serve as a foundation for future conceptual and empirical scholarship as well as policy-making. In addition, while it would be premature to declare the ethically “correct” approach for PCT-CF management in all instances, we hope that the considerations raised here will facilitate careful deliberation about actual cases as they occur in practice.

PCTs AND THEIR ETHICAL COMPLEXITY

PCTs are described as “pragmatic” rather than “explanatory” because they aim to understand how interventions work in real life (Tunis 2003). PCTs have three key attributes. First, they aim to “inform decision-makers (patients, clinicians, administrators, and policy makers),” rather than to explain a biological or social mechanism. Second, they “enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant” as opposed to traditional explanatory clinical

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trials that often fail to reflect the patients living with the condition under study. Third, they intend either to (a) “streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial” or (b) “measure a broad range of outcomes” (Califf & Sugarman 2015, 438).

By embedding research in settings where patients receive usual clinical care, PCTs can avoid the need for a separate, parallel research infrastructure—and its associated costs. Additionally, by capitalizing on existing data systems, such as electronic health records (EHRs), and expanding computer and analytic capabilities, PCTs enable the capture and analysis of far larger data sets than traditional clinical trials (Califf & Sugarman 2015). Consequently, PCTs are often able to generate evidence far more efficiently than could be done through conventional explanatory research.

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Despite these positive attributes, however, PCTs have presented an array of ethical and regulatory challenges (Califf & Sugarman 2015). Prior work has detailed several such challenges, including the appropriateness of modifying consent processes, the role of gatekeepers, and privacy, among others (Sugarman & Califf 2014). Some of these challenges arise through features of PCTs that challenge traditional conceptions of the boundaries between different activities, especially research, clinical care, and quality improvement. Historically, research oversight has been premised on the view that research and clinical care are distinct activities and merit different forms of oversight (Kass et al 2013). Embedding research into settings where care is usually delivered and studying widespread care practices has raised questions about the continued appropriateness of traditional regulatory and ethical frameworks that have relied upon drawing a sharp distinction between research and clinical practice (Kass et al. 2013; Faden et al. 2013)

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Assessing the appropriate ethical oversight and management of PCTs is further complicated by the heterogeneity of PCTs themselves. Different study designs are needed to answer different research questions, involving different types of engagement with both patients and clinicians (Ali et al. 2015). Consequently, PCTs involve a range of different activities and associated burdens for patient-subjects and other stakeholders. Some PCTs resemble routine quality improvement (QI) activities involving minor modifications of health care delivery that create only minimal risks, yet others involve substantial alterations to clinical care and care processes.

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Furthermore, several contextual factors raise particular challenges for the assessment and ethical management of PCT-CFs. First, PCTs may be conducted without the explicit consent (and perhaps even awareness) of patient-subjects. Some may also be conducted without the consent or awareness of clinicians, such as PCTs examining clinician- or system-level interventions. The decision to not seek individual-level consent for PCTs may, in some cases, be justified on both ethical and regulatory grounds. For example, US federal research regulations permit a waiver or modification of consent when research involves no more than minimal risk, the waiver of consent will not adversely affect the rights and welfare of subjects, the research could not practicably be carried out without the waiver, and information about the research will be made known to the subjects as appropriate (45 CFR 46.116). Nevertheless, waivers of consent may complicate decisions about whether and how

to return information about a PCT-CF, since individuals may not have prior knowledge that they were in a PCT, much less have considered the potential they may receive individual-level health information as a result. Second, unlike IFs and SFs detected in standard medical practice or explanatory research, PCT-CFs may be identified by researchers without any prior relationship to an individual patient for whom the information may have clinical relevance. This raises both normative and practical considerations, as the nature and extent of a relationship may influence responsibility for disclosure of a PCT-CF as well as how such information might be delivered to and received by the individual about whom the information pertains. Third, PCTs are often of substantial scale, sometimes involving as many as hundreds of thousands of patients distributed across numerous clinic settings, which could translate into considerable effort and costs for health systems related to managing PCT-CFs; these may be especially challenging for clinicians within these health systems, many of whom may not have been directly involved in the PCT prior to the discovery of a PCT-CF.

THE INSIGHTS FROM—AND LIMITS OF—EXISTING SCHOLARSHIP AND GUIDANCE

While there has been considerable attention focused on the ethics of PCTs as well as cluster-randomized trials (Anderson et al 2015; Califf & Sugarman 2015; Weijer et al. 2011), which include some PCTs, we are unaware of any literature directly addressing the ethical management of PCT-CFs. Nevertheless, insights from several areas that each share some attributes of PCTs are informative. These somewhat analogous areas include: clinical care; quality improvement; clinical research; population genomics; environmental health research; and public health surveillance. Next, we describe each area along with its ethically relevant similarities and dissimilarities to PCT-CFs.

Clinical Care

IFs have been a longstanding issue in clinical care, particularly for diagnostic imaging and laboratory testing. In clinical practice, IFs are considered to be findings that are unrelated to the clinical indication for which a test was ordered, or, as framed by the American College of Radiology, findings that raise questions regarding the “responsible use of information that nobody asked for” (Berland et al. 2010).

Ethically Relevant Similarities to PCT-CFs—One key similarity between clinical care IFs and PCT-CFs relates to the importance of considering both the potential benefits and harms that may result from providing information about them to patients. Guidance documents regarding IFs in radiology have aimed to help clinicians differentiate benign from potentially serious findings, recognizing that follow-up can lead to a “cascade of testing that is costly, provokes anxiety, exposes patients to radiation unnecessarily, and may even cause morbidity” (Berland et al. 2010). While some IFs identify potentially serious health conditions, many do not and there is recognition that disclosing all IFs is problematic. Logistical barriers associated with disclosure include time constraints that distract patients and providers from “primary concerns” (Brown 2013) and the risk that limited

understanding of the implications of the information could leave patients feeling “overwhelmed or fearful” (Kang 2016).

One approach to balancing potential benefits and harms from disclosure is suggested by the American College of Medical Genetics and Genomics’ (ACMG) approach to secondary findings. Specifically, the ACMG advises that laboratories undertaking clinical sequencing interrogate and report on a defined set of 59 genes. The selected genes are those “considered most likely to be verifiable by other diagnostic modalities and amenable to medical intervention based on current evidence” (Green et al. 2012). The selected genes represent an effort to maximize the benefits (increasing the likelihood of true-positive, actionable results) while minimizing the harms (decreasing the likelihood of false-positive results) (Green et al. 2012; Kalia et al. 2016).

Ethically Relevant Dissimilarities to PCT-CFs—One key dissimilarity between PCT-CFs and clinical care IFs is often the nature of the relationship between the individual who identifies the finding and the person about whom that information pertains. As described by Miller, Mello, and Joffe, “The overall health of the patient is of primary concern to all physicians engaged in patient care” (p. 272). Further, the physician-patient relationship involves an assumption of physician responsibility for the patient’s health (Miller, Mello, Joffe 2008). This responsibility of physicians to patients is arguably distinct from that of researchers to participant-subjects.

An additional dissimilarity involves the role of informed consent in decision making about return of IFs/SFs and PCT-CFs. Prior recommendations for managing clinical IFs have emphasized that patients should decide in advance with their clinicians whether or not to learn about unexpected findings (Presidential Commission 2013; NAM 2018). Such recommendations have limited applicability to many PCTs, in which research subjects may not have been engaged in prospective discussion about their preferences related to participation, much less about disclosure of PCT-CFs.

Furthermore, the timeliness of an IF identified in clinical care may be quite different from PCT-CFs. For example, while a clinical radiology report is likely to be read soon after it is generated, a finding identified through data analysis for a PCT may not be discovered until months or even years later. This delay can influence not only clinical relevance, but also the feasibility of recontact and actually providing information about a PCT-CF.

Quality Improvement

Quality improvement (QI) in health care includes “systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings” (Lynn et al. 2007). QI activities may be instructive for PCT-CFs, as they each may involve similar design and risk levels, may assume an individual duty to participate, and raise related questions regarding the scope of obligations to individuals involved in them.

While there is a substantial literature regarding the ethics of QI, there is limited discussion regarding what results, if any, should be returned to individual patients. However, several statements from a Hastings Center working group on the ethics of QI are worth noting for

their potential applicability to PCTs (Lynn et al. 2007). First, the group argues that patients have a responsibility to cooperate with QI activities, and that this responsibility is not contingent upon whether a patient directly benefits from a specific QI activity. On their view, this responsibility exists because the care each patient receives is advanced by the collective cooperation of all patients in the overall quality enterprise. This obligation is distinct from that of research participation, in which participation generally should be voluntary, because QI “generally aligns with patient interests, presents lower risks than continuing with usual (clinical) care,...demands the participation of all to be effective, [and] arises from a responsibility of professionals and patients alike...” (Lynn et al. 2007).

The group also delineated a set of “Ethical Requirements,” which, based on respect for participants, states “participants in a QI activity should receive information about findings from the activity that are clinically relevant to their own care” (Lynn et al. 2007). However, further specification about the scope of such a disclosure or the corresponding process are not elaborated.

Ethically Relevant Similarities to PCT-CFs—The extent to which the QI context is informative for PCT-CFs will vary based upon the PCT study design. Some PCTs, such as those that evaluate systematic interventions to improve the organization or the delivery of health care, overlap in both goals and methods with QI activities (Finkelstein 2015). Consequently, the methods by which clinically relevant findings are generated may be similar in the two contexts. Similarly, some PCTs and QI initiatives may be implemented at the level of clinics or hospitals (or units within them), rather than at the level of individual patient-subjects.

Furthermore, like QI activities, there may be arguments that participation need not be voluntary for some PCTs, such as PCTs in a mature learning health system that do not present greater risks and burdens than usual care and for which opting out would undermine the scientific integrity and the corresponding ability of the system to undertake continuous quality improvement (Faden et al. 2013).

Ethically Relevant Dissimilarities to PCT-CFs—One important dissimilarity is that routine QI is typically conducted within a single institution or organization, whereas PCTs may involve broader collaborations and PCT-CFs may be identified by individuals without a prior relationship with the patient-subjects about whom data is collected. Consequently, the extent of obligations to advance the interests of patient-subjects may differ in large-scale PCTs compared to QI undertaken by clinical and operational leaders within a defined health system.

Yet PCTs may also differ from QI in ways that suggest obligations to individuals may be greater in the PCT context. For example, while routine QI typically involves low-risk activities to improve care within local contexts, PCTs can affect care in ways that may confer additional risks, including risks related to data collection (Finkelstein et al. 2015), which may in turn suggest greater obligations of reciprocity between researchers and subjects.

Clinical Research

Arguments for whether, when, and how to disclose IFs and SFs encountered in conventional clinical research are influenced at least in part by the nature of the researcher-subject relationship, including what duties researchers owe to subjects. Thus, the normative literature pertaining to researchers' duties, including those related to ancillary care, may be instructive for PCT-CFs.

Empirical and normative scholarship about IF/SFs arising in clinical research has largely centered on radiology and genomics. For example, an investigator using brain imaging in research regarding the pathophysiology of depression with healthy volunteers could detect a possible brain tumor (Miller, Mello, and Joffe 2008). In genetics research, researchers employing whole genome sequencing to identify the molecular cause of a suspected genomic condition might detect that a patient-subject harbors a genetic mutation associated with long QT syndrome, indicating an elevated risk for sudden cardiac death in an otherwise healthy individual, and therefore a need for medical management.

In general, the normative literature has concluded that researchers have obligations to disclose IF/SFs, but that this duty is "limited" in scope (Richardson & Cho 2008; Miller, Mello, Joffe 2008). Researchers' limited duties to disclose IFs arise in part from researchers' access to otherwise private information, which may create a duty of reciprocity. This limited duty owed to research subjects by researchers contrasts with the "robust duty of care" owed to patients by clinicians, including a duty to disclose information relevant to treatment decisions (Wolf 2013). This distinction derives from the different purposes of the two activities; unlike clinical care, in research, the primary goal is not to benefit the individual, but instead to produce generalizable knowledge (Joffe and Miller 2008). Thus, researchers are not typically held to owe participants the same duty of care as would be expected from a treating physician. However, empirical data suggest that neither patients nor Institutional Review Board (IRB) members necessarily share the view that researchers and clinicians hold distinct obligations. Specifically, several studies indicate that majorities of both patients and IRB members generally perceive researchers as having similar duties as clinicians in disclosing clinically relevant information to participant-subjects, at least in circumstances where data are clinically actionable (Faucett 2016; Gilwa 2016; de Boer 2018).

Several considerations have been suggested for determining the scope of researchers' duties. These include: the risks and benefits of disclosure, including costs; the vulnerability and the dependence of the subject on the research team; the impact of the disclosure on the generation of socially valuable knowledge; and the researcher-subject relationship, including both the nature and the extent of their engagement (Miller, Mello, and Joffe 2008; Richardson and Belsky; Richardson and Cho 2012).

More recently, the potential for IFs has also been addressed in the context of precision medicine, a domain that like PCTs, straddles the boundary between research and care (Minari, Brothers, & Morrison 2018). For example, genetically sequencing asymptomatic individuals to provide a reference point for patients with various conditions to evaluate the penetrance and pathogenicity of genomic variants may identify IFs with potential clinical relevance (Minari, Brothers, & Morrison 2018).

Ethically Relevant Similarities to PCT-CFs—Several themes related to research IFs and SFs may be informative for PCT-CFs. First, information discovered in some clinical research, as in PCTs, will be identified by researchers, rather than by treating clinicians. As described earlier, the nature of the relationship can influence the extent of duties related to the return of this information. Nevertheless, at least within the context of explanatory trials, there is now “quite a broad consensus” that investigators “should return IFs and individual research results (IRRs) when they are valid, clinically important, and actionable” (Morreim 2018). This consensus exists despite an apparent lack of agreement upon a theory or principles for when or why this should occur (Morreim 2018; Gilwa 2016), or regarding the definition of “actionable” for these purposes (Berg, Amendola, Eng et al. 2013). This is consistent with arguments articulated in deliberations about genomic research that there is an obligation to return research findings that have utility for persons (Brothers et al. 2019).

However, there is also broad recognition of the trade-offs associated with the decision to return IFs in clinical research. For example, responsible return of IFs requires additional time and resource investments associated with contacting participants, counseling, and potential clinical follow-up. A decision to return IFs therefore has opportunity costs for the research enterprise, slowing scientific discovery, which represents a potential harm to research investigators, participants, institutions, and the broader public (NASEM 2018). These opportunity costs are likely to be considerable in the context of large-scale PCTs.

Scholarship regarding IFs in biobanking research and research with stored specimens, may be particularly instructive for PCT-CFs, as these types of research share at least two key similarities to PCTs. First, the participant/subject-researcher relationship, like in PCTs, is typically more distal than in explanatory research. On point, it has been suggested that the limited extent of engagement between researchers and participants in biobanking research as compared to traditional research may lessen the scope of obligations to disclose IFs (Richardson and Cho 2012). A similar argument could be made for PCTs, particularly in circumstances in which subjects are not solely dependent on the research team for receiving clinical care. Second, challenges associated with contacting biobank participants to return findings parallel those that would likely be faced in at least some PCTs. This issue has been deemed the problem of the “cold call,” as described by the following vignette:

You were a patient at Hospital A several years ago when you were suffering from disease X, which has long since resolved. You have just arrived home from a long day’s work when the phone rings. When you answer, a soothing voice says, “I am a scientist at Research Institution B two time zones away. I was examining your DNA and found a variant associated with Disease Y that may be really important for your health. Do you want to know about it?” If the scientist were particularly thoughtful, she might ask, “Can you come here for genetic counseling?” You wonder, What is DNA? How did she get mine? What is a variant? What is Disease Y? What is genetic counseling? Who is going to pay for me to go to Research Institution B? Most important, you think, What choice do I have? (Clayton 2008, 286).

A similar “cold call” challenge may arise in PCTs, in which researchers inquiring of patient-subjects whether they wish to learn about a PCT-CF, might have to first disclose that a PCT itself had, in fact, previously occurred.

Ethically Relevant Dissimilarities to PCT-CFs—While discussions about researchers’ duties related to return of IFs and SFs in explanatory research suggests some relevant considerations for PCTs, several features of PCTs raise questions about the extent to which guidance from the explanatory research setting might be appropriate for PCT-CFs. First, as described previously, by embedding research into settings where routine clinical care is delivered, PCTs may disrupt traditional research norms that are premised on research and care as distinct activities—including norms pertaining to researchers’ obligations to return potentially clinically relevant information to individual participants. Decisions over how to return PCT-CFs therefore represent what Susan Wolf has termed elsewhere as a “bridge problem,” challenging the dichotomy between research and clinical care that ethics and law have long embraced (Wolf 2013). This dissimilarity, however, is not unique to PCTs, but may instead reflect broader shifts in perceptions regarding the ethical obligations of researchers to participants (Brothers et al. 2019).

A second key dissimilarity for PCT-CFs from IFs/SFs in explanatory research, including research involving biobanks and stored samples, is that existing guidance for explanatory trials has generally assumed—and emphasized—the role of consent. Consent, it is argued, can demonstrate respect to participants, alerting them to the possibility for IFs/SFs and to the planned approach for their management, as well as potentially offering participants a choice about the return of specific types of findings.

The emphasis on consent suggests a potential key dissimilarity for some PCTs. As noted earlier, patients may not even be aware of their participation in these studies, much less have been explicitly asked to participate. Consent thus seems ill-suited to play a central role in ethical management for at least some PCT-CFs.

An additional dissimilarity pertains to the validity of research test results. For example, there has been substantial discussion about tests done in research that are generally not performed in accordance with established clinical laboratory practices, especially Clinical Laboratory Improvement Amendments requirements for testing to be used for clinical decision making (NAM 2018). This debate likely has limited applicability for PCTs, which are embedded in clinical operations, and typically rely on clinical laboratory and imaging data.

Population Genomics

Population genomics examines variation across genomes and populations to discover “knowledge about genetic disorders, possible cures, and the origin and migration patterns of distinctive peoples” (McGregor 2007, 356). Prior scholarship has examined challenges that share parallels to those that may arise from PCT-CFs, including those related to return of individual results, as well as group-level impacts. At the individual level, Iceland’s deCODE Genetics population database was able to identify thousands of women with a greater than 80% risk of breast and/or ovarian cancer associated with BRCA2 mutations—some of whom had not participated in genetic testing, but for whom risk was identified by imputing genotypic data (Gitter 2019). At the group-level, projects may identify that members of certain groups are at elevated risks for some conditions, which might contribute to stigmatization (Foster & Sharp 2006). They also may present culturally specific risks, such

as when genetic research with samples from the Havasupai tribe undermined the group's origin story (McGregor 2007).

Ethically Relevant Similarities to PCT-CFs—One key similarity of IFs/SFs in population genomics research to PCT-CFs is that the impacts of disclosure of information in both circumstances may extend beyond individuals to include impacts for third parties and groups (McGregor 2007). While researchers have limited control over these issues, recommendations from Foster and Sharp that researchers take care to appropriately frame findings seems similarly apt for PCT-CFs, particularly for cluster-level findings. Additionally, akin to biobank research, findings may be identified by individuals with only distal relationships to the patient-subjects.

Ethically Relevant Dissimilarities to PCTs-CFs—Scholarship on population genomics has, like for clinical research, typically emphasized the importance of informed consent and respect for participants' preferences when deciding whether to return findings to individuals. As discussed previously, this guidance has limited applicability for PCT-CFs.

Environmental Health Research

Environmental health research can discover information that may be relevant to protecting the health and safety of research subjects and third parties, some of which is likely to be beyond the scope of the research question. In this way, it shares potential parallels to PCT-CFs. For example, research that collects allergen samples in the home for an asthma study might observe potential health hazards unrelated to the study, such as mold (Resnick & Zeldin).

Five criteria have been proposed for determining the scope of researchers' obligations to participants in environmental health research regarding health risks encountered beyond those of the study purpose: evidence for the risks; nature of the risks (e.g., possible adverse health effects and their severity); usefulness of the information to subjects; effects on the study from informing the subjects (e.g., impact on scientific integrity); and effects on the target community from informing the subjects (Resnick). These criteria are notably similar to those proposed for conventional explanatory clinical research.

Ethically Relevant Similarities to PCT-CFs—As in clinical research, findings in environmental health research will be identified by researchers, rather than those involved in the delivery of clinical care. Therefore, obligations to return such information will be influenced by the scope of researchers' duties to participants. Arguments related to the scope of researchers' duties for environmental health research parallel those made in the normative literature regarding researchers' duties related to ancillary care (Richardson and Belsky). Resnick and Zeldin argue that while environmental research creates special duties to participants, those duties are limited to the scope of the research inquiry. They offer three reasons to justify that scope: researchers' lack of expertise to address risks unrelated to the research aims; researchers' lack of time or resources to address risks unrelated to research; and that research subjects do not normally expect investigators to deal with risks unrelated to research. At least the first two reasons seem relevant to PCT-CFs. First, researchers in PCTs

may not have clinical expertise relevant to the finding in question, limiting their ability to independently determine its potential clinical relevance, much less appropriately counsel a patient regarding needed clinical follow-up. Second, resource constraints are arguably similar and perhaps even especially relevant for PCTs, which may include thousands of patient-subjects, and therefore present extensive logistical and resource challenges to returning PCT-CFs. With respect to the third reason, it is not yet known whether individuals in PCTs expect investigators to address risks unrelated to research.

An additional similarity of findings in environmental health research and PCTs is the issue of delayed identification and analysis of individual research results that may have potential health implications for participant-subjects. Consider, for example, the lawsuit associated with the Kennedy Krieger Institute (KKI) study on lead abatement for housing in Baltimore, MD. Among the plaintiffs' complaints was that KKI researchers failed to warn parents in a timely fashion of dangerous lead exposures (Resnick and Zeldin). Yet, as KKI noted in a related legal brief, as the tests were being conducted for research purposes rather than clinical decision-making, they were done in large batches with a typical turn-around time of several months—a time lag that could limit their relevance for both prevention and for subsequent clinical decision-making (Hoffman & Rothenberg). Similar challenges have been identified for environmental epidemiological research of exposure biomarkers, which are typically measured long after sample collection, creating uncertainty regarding the relevance to current exposure (Salerno et al.). Comparable issues related to the timeliness of findings are likely to be encountered in PCTs, in which analysis may occur months if not years after the initial test or event.

Ethically Relevant Dissimilarities to PCT-CFs—One potentially notable dissimilarity between environmental health research and PCTs relates to the nature of the study finding and how easy the implicated health condition is to prevent or control. With environmental risks, individuals might be able to leave a particular setting to reduce or prevent the impact of exposure, but it may be more difficult to avoid or mitigate the effects of internal risk factors identified in PCTs.

Public Health Surveillance

Public health surveillance involves the collection of data “with the intent of enabling public health action, whether direct intervention, priority-setting, resource allocation, or advocacy” (WHO 2017). Public health surveillance poses similar questions as those encountered in PCTs as well as QI regarding what constitutes “fair exchange” or reciprocity. In such circumstances, the individuals about whom information is shared—generally without their permission—may not be among those who benefit. Debates about how to best address this challenge have arisen in various public health contexts, including debates over blinded seroprevalence studies in the early years of the HIV/AIDS epidemic, (Bayer, Lumey, and Wan 1990; Isaacman 1993), and more recent questions about whether to notify blood donors regarding identification of sickle cell trait and communicable diseases (e.g., HIV, Hepatitis B and C, and syphilis) (Lee & Marks 2014).

Ethically Relevant Similarities to PCT-IFs—Debates over public health surveillance parallel PCTs in that the scale and nature of the research may be sufficiently large so as to render return of individual findings infeasible. For example, while the International Guidelines for the Ethical Review of Epidemiological Studies states that “part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health, the guidelines also acknowledge the potential “impossibility of communicating study results.” In such cases, the guidelines state that “the ethical duty to do good can be served by making pertinent health care advice available to their communities” (CIOMS 1991). In PCTs, a similar argument might support a decision to return aggregate findings to the health system, rather than to individuals.

Ethically Relevant Dissimilarities to PCT-IFs—One important dissimilarity between public health surveillance and PCTs relates to the purpose of the activities. As argued in WHO’s 2017 ethical guidelines, while the methods of public health surveillance may share parallels with epidemiology research, it is “not simply another form of research” for, among other reasons, the subject of the concern for surveillance is a community, rather than individuals (WHO 2017). This contrasts with traditional research with human subjects, in which the subject of concern is commonly the individual. Thus, it is widely argued in public health surveillance that the needs of the public may, at times, override individual-level preferences, including not permitting individuals to opt out of reporting, based upon both the scientific need to avoid selection bias as well as normative concerns related to the fair distribution of benefits and burdens (WHO 2017).

SUMMARIZING THE RELEVANT ATTRIBUTES FOR PCT-CFS

Our review suggests important considerations for assessing and managing PCT-CFs in an ethically appropriate manner. Below, we outline these considerations, as well as the degree to which prior normative recommendations for decision-making might be appropriately used for PCT-CFs.

First, *what* is the nature of the finding? What is the severity, certainty, and broad actionability of the finding (where “actionability” refers to whether clinicians or individuals can make use of or act upon the findings)? Is that finding relevant for diagnosis, treatment, or prevention? How much difference would disclosure of the PCT-CF make to the individuals’ health and well-being? (Richardson 2008) From our review, there seems to be consensus in other settings that findings that are severe, valid, and clinically actionable weigh more heavily towards disclosure than do findings that are less severe, less certain, or less clinically actionable; however, there is, as yet, little agreement regarding the theoretical basis upon which this consensus rests. Notably, these criteria are fairly consistent across contexts, despite the fact that these literatures have largely not been in conversation with one another.

Second, *when* was the finding identified? For example, EHR data analyzed in a PCT may identify PCT-CFs a year or more after their initial presentation, potentially influencing their clinical relevance and actionability. At least three time points are relevant: when the data

were obtained, when they were analyzed, and when a PCT-CF was recognized. While this issue has previously been identified within environmental health research, no clear normative principles emerge from the literature with respect to how timing might inform considerations related to the ethical management of PCT-CFs.

Third, *where* did the finding occur? Although we did not identify any prior scholarship engaging this question, the location of the finding seems to be a central consideration for management of PCT-CFs. For example, a finding discovered in the context of a fee-for-service health system may arguably generate different obligations than those within an integrated delivery system with an expressed commitment to the health of its covered population. Similarly, there may be morally relevant differences based upon whether the PCT-CF was identified by the institution at which the patient-subject receives care, rather than by an outside research entity.

Fourth, *why* and *how* did the finding arise? How was the PCT designed? Was consent obtained? Was it randomized at either an individual or cluster level? How similarly does the study approximate standard clinical care as compared to explanatory research? Prior ethics scholarship on QI and ethical obligations related to IF/SFs arising from clinical research suggests several considerations. For example, arguments that the obligations owed by researchers to subjects are distinct from those owed by physicians to patients may suggest that a stronger duty to return PCT-CFs exists for PCTs that more closely resembles clinical care than PCTs that are more akin to explanatory trials. However, PCTs that involve interventions that deviate from standard clinical care may also imply greater duties of reciprocity to patient-subjects than those that are observational.

Fifth, *who* knows the information? What is their relationship to the individual about whom the information pertains, and how dependent is the individual on the research team for learning the information and receiving clinical follow-up, if appropriate? As Henry Richardson has observed elsewhere, the fact that an individual has “found” information does not necessarily mean that the information was not already known by someone else, including perhaps even by the individual about whom that information pertains (Richardson 2008). Researchers’ duties related to PCT-CFs are arguably stronger when the information is uniquely known by the research team, rather than by other individuals (Richardson 2008).

REMAINING QUESTIONS AND NEXT STEPS

While existing scholarship can provide some guidance on PCT-CFs, numerous issues and questions remain. One issue pertains to the liminal nature of PCTs. As PCTs straddle the boundary of research and clinical care, determining roles and responsibilities regarding PCT-CFs challenges traditional scholarship predicated on viewing the two domains as distinct. Similarly, while we have focused here primarily on individual-level CFs, PCTs can generate both individual- and cluster-level CFs, which creates further complexity, particularly with respect to their management. These issues warrant careful conceptual scholarship and deliberation.

Additional questions also exist regarding potential hazards associated with the return of PCT-CFs. Here, experience related to performance reporting of health systems may be instructive. In brief, public reporting, some argue, can support the delivery of high-quality, cost-effective care, helping patients and payers identify the highest quality providers, and enabling providers to benchmark their performance against their peers (Metcalf et al. 2018). However, several issues have been documented related to downstream implications resulting from that reporting. For example, failing to appropriately adjust for case mix differences might lead to misleading conclusions, labeling providers that treat higher-risk patients as poor performers (Metcalf et al. 2018). It may also lead to “cherry picking,” with providers preferentially selecting lower-risk patients (Werner & Asch 2015). This preferential selection can, in turn, create access challenges, particularly for patients with high health needs (Jacobs, Cerfolio, & Sade 2009). Similar challenges might arise from disclosure of cluster-level PCT-CFs, if appropriate adjustments are not made for differences in case mix. Accordingly, these considerations should be taken into account as plans are made to disclose PCT-CFs.

Similarly, additional insights might be gained from engaging with those charged with overseeing patient safety and error disclosure. For example, literature on error disclosure suggests that the individual best situated to disclose an error to an affected patient may vary based upon the nature of the error and the context in which it occurred (Gallagher et al. 2015). This literature may suggest important considerations regarding who should disclose PCT-CFs, and the appropriate modality for such disclosures.

In addition, empirical research could meaningfully inform the analyses of some of these issues. Several areas seem particularly ripe for empirical work. First, what are the attitudes of prospective patient-subjects? For example, do prospective subjects have different preferences for disclosure of information based on how the information came to be known, such as whether it arose during routine clinical care as opposed to being discovered through QI or research? Do they acknowledge and value the trade-offs associated with disclosure of a PCT-CF, including its impact on other clinical or research activities? Do their preferences differ based upon the type of finding, such as whether it relates to prevention of a future health risk versus treatment of an existing condition? Additionally, in the event that a health system decides to return a PCT-CF, how would they prefer that disclosure to occur? Do they prefer to receive the information directly, or should it be mediated through their clinical provider?

Similar questions are relevant with respect to the perspectives of other stakeholders, including payers, quality improvement specialists, health systems, sponsors, and IRBs and others charged with ensuring appropriate research oversight and governance. When assessing such perspectives, it would be particularly useful to elicit attitudes and beliefs regarding where the decision-making authority for management of PCT-CFs should reside. Are such decisions appropriately managed by researchers, IRBs, operational leadership, or perhaps through some combination of these groups?

CONCLUSION

PCT-CFs have similarities to findings that arise in other somewhat analogous contexts. However, they also differ in ethically important ways. In this paper, we have described the ethically relevant similarities and dissimilarities of these other contexts to PCTs, and identified relevant attributes to guide the identification, assessment, and management of PCT-CFs. Given the heterogeneity of PCTs, there is unlikely to be clear “one-size-fits-all” approach that is appropriate for every PCT-CF. Moving forward, stakeholders should develop a typology to guide decisions based on the specific context of a PCT. Ideally, these decisions should be considered *prospectively*, before a PCT is initiated. Regardless, developing guidance for the prospective management of PCT-CFs will be critical for fulfilling the promise of PCTs to drive efficient generation of evidence to improve individual and population-level health.

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Table 1.

Ethically relevant similarities and dissimilarities from existing scholarship on areas sharing at least partial analogies to the PCT context.

CONTEXT	SIMILARITIES to PCTs	DISSIMILARITIES to PCTs
Clinical Care	<ul style="list-style-type: none"> Need for considering both the potential benefits and potential harms associated with disclosure of findings (for patient-subjects, clinicians, and broader clinical and/or research systems) 	<ul style="list-style-type: none"> Physician-patient relationship distinct from that of researcher-subject; scope of researcher duties to subject may be more limited than those of physicians to patients Individual informed consent may not have occurred for a PCT, limiting its ability to ensure concordance with a subject's values & preferences regarding disclosure of findings Timeliness in identification; PCT-CFs may be identified long after data were collected, limiting their clinical utility
Quality Improvement	<ul style="list-style-type: none"> May involve similar methods and (low) level of additional risk May assume an individual duty to participate, at least within some circumstances; may not solicit individual informed consent 	<ul style="list-style-type: none"> Routine QI typically conducted within a single institution, whereas PCTs more likely to involve multi-institution collaborations, with corresponding implications for the extent of institutional obligations to individuals about whom the information pertains Some PCTs may confer additional risks, suggesting greater obligations of reciprocity between researchers and subjects
Clinical Research	<ul style="list-style-type: none"> Findings are identified by researchers, who may have more limited duty to benefit individuals than do physicians Decisions about disclosure involve consideration of trade-offs for subjects, clinicians, health systems, and the research enterprise In biobanking and research with stored specimens: researcher-subject relationship may be similarly distal, potentially lessening the scope of obligations to return results, and may similarly present challenges of the "cold call," in which disclosure of findings also requires disclosure of the research activity itself 	<ul style="list-style-type: none"> PCTs are embedded into clinical care, which may undermine arguments that researchers have more limited duties to disclose than physicians Individual informed consent may not have occurred for a PCT, limiting its ability to ensure concordance with a subject's values & preferences regarding disclosure of findings
Population Genomics	<ul style="list-style-type: none"> Impacts of disclosure may affect third parties as well as individuals; concern for findings impacting stigmatization Researcher-subject relationship likely distal, potentially lessening the scope of obligations to disclose findings 	<ul style="list-style-type: none"> Individual informed consent may not have occurred for a PCT, limiting its ability to ensure concordance with a subject's values & preferences

CONTEXT	SIMILARITIES to PCTs	DISSIMILARITIES to PCTs
Environmental Health Research	<ul style="list-style-type: none"> Findings identified by researchers, who may have lesser duties to benefit individuals than do physicians Resource constraints may influence decisions about disclosure of findings, given potentially extensive number of affected individuals Identification of findings in each context may be delayed, which may in turn limit the clinical utility of their disclosure 	<ul style="list-style-type: none"> Environmental health risks may be easier to prevent or control than internal risk factors identified through a PCT
Public Health Surveillance	<ul style="list-style-type: none"> Scale and nature of research may be sufficiently large as to render return of individual findings infeasible 	<ul style="list-style-type: none"> Purpose of the activity or research being conducted (collective good vs individual health improvement)