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Returning Individual Research Results from Digital Phenotyping in Psychiatry

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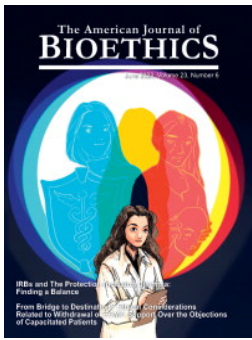
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






















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Returning Individual Research Results from Digital Phenotyping in Psychiatry

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ABSTRACT

Psychiatry is rapidly adopting digital phenotyping and artificial intelligence/machine learning tools to study mental illness based on tracking participants' locations, online activity, phone and text message usage, heart rate, sleep, physical activity, and more. Existing ethical frameworks for return of individual research results (IRRs) are inadequate to guide researchers for when, if, and how to return this unprecedented number of potentially sensitive results about each participant's real-world behavior. To address this gap, we convened an interdisciplinary expert working group, supported by a National Institute of Mental Health grant. Building on established guidelines and the emerging norm of returning results in participant-centered research, we present a novel framework specific to the ethical, legal, and social implications of returning IRRs in digital phenotyping research. Our framework offers researchers, clinicians, and Institutional Review Boards (IRBs) urgently needed guidance, and the principles developed here in the context of psychiatry will be readily adaptable to other therapeutic areas.



KEYWORDS

Research ethics;
psychiatry/psychology;
neuroethics; human
subjects research

INTRODUCTION

A University research team is developing an app to conduct a digital phenotyping study of mental illness in young adults. The goal of this study is to better understand the factors that increase or decrease the likelihood of symptoms of severe mental illness, paving the way for more effective interventions. Using smart watches and smart phones, multiple streams of data will be collected and then analyzed by artificial intelligence/machine learning: GPS location, phone/screen/Internet usage, phone logs, text logs, and content of social media posts, web search queries, and text messages; sleep, 24/7 continuous measurement of movement and physical activity, and heart rate. Virtual

video interviews with the research team will deploy multiple validated clinical instruments. In addition to knowing when symptoms of mental illness are abating or rising, the research team also anticipates that they will likely be able to know other information, for example when participants are involved in activities such as using illicit drugs, having sex, buying liquor, driving while drunk, visiting pornography websites, and having suicidal ideations. The digital phenotyping research team has the technology to facilitate return of individualized results to each participant, on a monthly, weekly, daily, or even more frequent interval. But the research team is unsure about how to formulate its protocol for return of Individual Research Results (IRRs), especially since the research may have

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concurrent validity (i.e., the relationship between past observed behavior and mental states), but will not yet have predictive validity (i.e., the ability to predict future behavior and mental states). The researchers need to know: When, in what format, and with what additional guidance should IRRs be returned to participants in this digital phenotyping study of mental illness, if at all?

The question posed in this opening vignette is urgent as psychiatric research and practice are rapidly embracing digital phenotyping methods (Gratzer et al. 2021; Torous et al. 2019; Liang, Zheng, and Zeng 2019; Onnela and Rauch 2016). Data gathered from smart phones, smart watches, other wearables, implantables, social media, and virtual-reality (VR) activity, combined with additional individualized data such as brain scans (Ressler and Williams 2021; Camacho et al. 2021) and clinical assessments (Baker et al. 2018; Torous et al. 2016) may lead to transformative clinical applications (Huckvale, Venkatesh, and Christensen 2019; Onnela 2021). Digital phenotyping in psychiatry utilizes large multimodal datasets to assess and even predict mental conditions. Digital phenotyping also offers researchers opportunities to intervene in real time to modify participant behavior and may necessitate high-stakes decision-making about returning results on a short timeframe, thus presenting novel issues in returning IRRs that are critical to address.

Digital phenotyping has been defined by Torous et al. (2016) as the “moment-by-moment quantification of the individual-level human phenotype in-situ using data from smartphones and other personal digital devices” and more broadly by Martinez-Martin

et al. (2018) as “approaches in which personal data gathered from mobile devices and sensors ... [are] analyzed to provide health information.” In this article we use the term “digital phenotyping” broadly to refer to research that might combine some or all of (1) smart phone and social media data; (2) data from wearables and implantables, (3) data from ambient sensors such as smart home sensors; (4) brain data, including magnetic resonance imaging (MRI), electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS) and other modalities; and (5) clinical assessments. The term “digital phenotyping” has become a term of art in multiple fields, and as this list shows, includes non-digital assessments such as biological measures and clinical assessments as potential components of digital phenotyping. We include clinical assessments because current research is already utilizing data from wearables alongside, and integrated with, more traditional clinical assessments (Torrado et al. 2022). As Melcher, Hays, and Torous (2020) have pointed out in the context of college mental health, “Data from smartphones *paired with clinical assessment data* can reveal what behaviors or combination of behaviors are correlated with mental health problems ...” [emphasis added]. The specific clinical assessments to be included in a digital phenotype will vary across research contexts. Our broad definition of “digital phenotyping” can be read to overlap with alternative terms such as deep phenotyping, computational phenotyping, deep biobehavioral-typing, and deep geno/-phenotyping (Baker 2019; Shen et al. 2022). We also use the term phenotyping in this article interchangeably with “phenotypic assays” and “phenotype”.

Box 1. Examples of data streams for digital phenotyping research in psychiatry.

| | |
|---|--|
| <p><i>Data from smart phones or computers:</i> GPS (latitude, longitude, and precision) Screen capture of phone activity Phone/screen usage (screen on/off time, reboots, apps used) Phone logs Text messages Hashed nearby WiFi router addresses and signal strength; Bluetooth data Social media content Virtual reality behavior</p> | <p><i>Data from wearables:</i> Accelerometer data (x, y, z acceleration) Brain activity, via noninvasive wearable Heart rate</p> |
| <p><i>Data from in-person, phone, or video engagement with members of the research team:</i> Interviews, including voice and facial movement data Validated clinical questionnaires/instruments Brain activity, measured through MRI</p> | <p><i>Data from ambient sensors, e.g., thermal sensors, acoustic sensors:</i> Movement Daily routines Voice and speech</p> |
| | <p><i>Data from apps / web-based platforms:</i> Cognitive tests Self-report surveys</p> |
| | <p><i>Data from implantables:</i> Brain activity Cardiovascular activity</p> |

Note. The data streams listed in Box 1 are illustrative, not exhaustive. The category headings illustrate some of the primary mechanisms by which data may be collected, but these headings are not mutually exclusive, e.g., we list GPS under smart phones, but GPS can also be collected from wearables and implantables.

Digital phenotyping offers an opportunity to collect and analyze multimodal individualized data streams of real-world behavior (Jain et al. 2015; Baker et al. 2018; Huckvale, Venkatesh, and Christensen 2019) and virtual-reality behavior (Freeman et al. 2017). A digital phenotyping study in psychiatry might include many different types of data streams, some potentially collected continuously and in real time (Box 1). For instance, so long as a participant's GPS-enabled smart phone is near them, that participant's location data is available to the research team. In addition, there is a range of passive and active data collection involved in phenotyping research. Once an app, for instance, is installed and preferences on data sharing are set, participants' GPS data is sent to the research team passively. By contrast, that same participant might be actively responding to daily questions about mood.

Advocates of digital phenotyping for psychiatric research suggest that digital collection of real-world data might offer the possibility of increased participant pools, lower costs, and continuous and perhaps more objective data on psychiatric symptoms (Smith 2018; Miller et al. 2022). Although digital phenotyping approaches are being explored in many areas of medicine including oncology (Blom et al. 2021), cardiology (Nasir and Khera 2020), and surgery (Jayakumar et al. 2020), we focus here on the use of digital phenotyping in mental and behavioral health (Davidson 2022; Hsin et al. 2018), with considerations that can be applied to other fields.

Disorders in psychiatry are often defined as patterns of behavior, but reliable data on real-world behavior have been elusive using traditional methods (Insel 2017), and therefore digital phenotyping offers distinct advantages. Widespread collection of real-world behavioral data, however, raises ethical and legal issues because psychiatric data are often sensitive and potentially stigmatizing; psychiatric disease severity may directly impact decision making capacity and self-awareness (e.g., during a manic episode or severe psychosis); and digital phenotyping data, such as data suggesting illicit drug use or suicidal ideations, may have legal implications including criminal prosecution, involuntary hospitalization, or third-party interventions such as "wellness checks" by police or emergency services.

In this article, we address a challenging and unresolved issue in digital phenotyping: the return of specific individual research results (IRRs). Return of individual and aggregate research results is a well-known issue (The Multi-Regional Clinical Trials (MRCT) Center 2017, 2023; Burke, Evans, and Jarvik

2014; Lévesque, Joly, and Simard 2011). Multiple scholars have argued that there is an ethical duty to allow participants to receive results in certain types of research (Knoppers et al. 2006; Faucett and Davis 2016), and multiple empirical studies clearly show that when asked, participants overwhelmingly express a desire to have individual research results returned (Facio et al. 2013; Yu et al. 2013). The advent of digital health data, along with more calls for open science, has increased the urgency and interest in addressing this return of results issue (Wong, Hernandez, and Califf 2018; Botkin et al. 2018). But although a growing body of research on the ethical, legal, and social implications (ELSI) of digital phenotyping has emerged (Martinez-Martin et al. 2018; Khodyakov et al. 2019; Torous et al. 2016; Nebeker, Bartlett Ellis, and Torous 2020; Marsch 2018), the literature has yet to provide guidance for how digital phenotyping results should be returned in real-world settings.

To address this gap, we convened an interdisciplinary, multi-institutional, expert working group, supported by the National Institute of Mental Health (NIMH). The working group began its work with consideration of existing ethical and legal guidance. In genetics and genomics, considerable progress has been made in establishing principles and guidelines for when and how to share individual and group research results, as well as incidental findings, with participants (MRCT Center 2017, 2023; Clayton and McGuire 2012; Holm et al. 2014; Wolf et al. 2008; Jarvik et al. 2014). These established guidelines and the emerging norm of returning results in participant-centered research meaningfully inform return of results in digital phenotyping research but are insufficient on their own.

Informed by existing recommendations on the return of research results generally, with particular focus on return of results in genetic research (MRCT Center 2017, 2023; Jarvik et al. 2014; Botkin et al. 2018; Burke, Evans, and Jarvik 2014; Clayton and McGuire 2012; Holm et al. 2014; Knoppers et al. 2006; Wolf 2013; Lázaro-Muñoz, Torgerson, and Pereira 2021), we developed an ethical framework for return of IRRs in digital phenotyping research in psychiatry. We do not claim here that return of IRRs in digital phenotyping is categorically unique. Indeed, as we discuss below, many challenges associated with return of IRRs in genetics/genomics are present in return of IRRs in digital phenotyping research in psychiatry, including uncertainty about the validity of IRRs, effective communication of complex results to

participants in meaningful ways, and the impact of return of IRRs on third parties such as family members. But we do argue that several features of return of IRRs in digital phenotyping research in psychiatry distinguish it qualitatively and quantitatively from return of IRRs in genetics, including: the many streams of IRRs that could be returned, at many intervals (weekly, daily, hourly); the ability of digital phenotyping IRRs to change behavior in both intentional/foreseen and unintentional/unforeseen ways (as compared to return of genetics IRRs, which does not change the genotype); and the wider population of people that may be affected by return of IRRs.

We begin by proposing a defined, common terminology to guide researcher decision-making and institutional review board (IRB) review of return of IRR policies. With key definitions in place, we then discuss several aspects of digital phenotyping research that have implications for decisions about return of IRRs. We present a novel Framework for Returning IRRs in Digital Phenotyping Research. The framework is grounded in the core bioethics principles of balancing benefit vs. risk, respect for persons, and promoting justice in returning data. We recommend how the framework can be used to foster dialogue around the Who, What, Where, When, and How of returning results in digital phenotyping research.

TERMINOLOGY

We recommend using a defined, common terminology to inform researcher decision-making and institutional review board (IRB) review of return of IRR policies. There is significant variation in the terms used to describe both research methods (e.g., digital phenotyping, computational phenotyping, computational psychiatry) and the content to return (e.g., results, data, raw data, interpreted data, information of value). Establishing consistent, defined, and shared terminology is important for effective communication and decision-making within and between research teams, IRBs, clinicians, and participants.

In [Table 1](#) we present definitions for key language relevant to return of IRRs in digital phenotyping in psychiatry. In laying out these terms, we aim to articulate meaningful differences within concepts that merit special consideration when returning results.

Our proposed terminology makes clear that the term “data” is not synonymous with “result.” Data is a term that, without qualification, can lead to unnecessary confusion. We suggest differentiating “data” from “raw data,” “processed data,” and

“interpreted data,” and then various sub-categories of “results” ([Table 1](#)). While categorizing data may sometimes be difficult, there are meaningful differences that will advance clarity in determining the details of a return of IRRs protocol and the language and methods to be deployed in communicating with participants throughout the research process.

The key distinction between raw and processed data is that the latter have undergone cleaning and processing. Processing of data may be conducted by multiple parties, including the research team, automation with AI/ML, a third party, and/or the research participant themselves. Examples of initial processing include using raw GPS location data to count the number of times someone left the house and using accelerometer data to track how many steps walked in a day.

The distinction between processed data and interpreted data is that, through analysis and interpretation, the processed data is given meaning. For example, a summary of the number of hours slept per day would be processed data, but it would become interpreted data (and hence a “result”) when that average sleep number is compared to the individual’s previous sleep patterns, compared to a national average, or used (in conjunction with other interpreted data) to make a diagnosis.

Some processed data are analyzed by automated pipelines or algorithms without a human reviewing the data first and may thus create different moral obligations than manually processed data. To illustrate, researchers are gaining the capability to apply artificial intelligence techniques to large amounts of personal sensor data in order to detect mood, affect, and the presence of mental disorders (Mohr, Zhang, and Schueller 2017). Supervised learning, unsupervised learning, and deep learning techniques are expanding in this space, but as Mohr, Zhang, and Schueller (2017) note, “the availability of easy-to-use tools for machine learning is expanding faster than the expertise, resulting in a growing number of publications using questionable methods.” For return of IRRs, the implication is that more caution may be warranted in returning data and results that were processed solely by a machine learning tool without a human in the loop.

A “result” is interpreted data at the individual or group level. We define an “Individual Research Result” as any “result” (i.e., “interpreted data”) or “finding” (primary, incidental, secondary, exploratory) about the individual research participant collected or generated by the research team as part of the research

Table 1. Definition of terminology related to returning IRRs in digital phenotyping research, presented in alphabetical order.

Actionability: The degree to which an individual research result can be used to guide decision-making (ACMG Board of Directors 2015). A result is generally considered to be “clinically actionable” if there are established therapeutic or preventive interventions available, or other available actions that can or should be taken on the basis of the result that may change the course of disease. A result with personal utility can also be actionable if the result may be of value to an individual, now or in the future, for purposes of guiding decision-making other than for diagnostic or therapeutic reasons (e.g., preparation for the future) (MRCT Center 2017).

Data: An umbrella term that can refer to the following types of data:

- *Raw data* are the direct output of data collection from sensors or active measures—the input to any data processing streams or data analyses.
- *Processed data* are data that have been filtered, summarized, converted, or transformed to allow for subsequent analysis and interpretation.
- *Interpreted data* are the “result(s)” at the individual or group level. The analysis and interpretation may be made by a human, automated process or algorithms (e.g., AI), or both, and the interpretation may explicitly include a comparison. Interpreted data may be compared to some sort of normative/statistical or other comparison model or values (including the mean) to classify, diagnose, or “score” a person, or place their values along a distribution (normal or otherwise) with respect to other people, other timepoints, or other data types.

Data Collection: Data in digital phenotyping are collected by active, passive, and/or mixed active-and-passive means.

- *Active Data Collection* is data collected from the research participant when the participant is aware of and engaged in the data collection process (e.g., completing a survey, performing cognitive testing, responding to interview questions).
- *Passive Data Collection* is data collected “without the active participation” of the participant (D. Mohr, Shilton, and Hotopf 2020) (e.g., continuous activity capture, monitoring of social media posts, GPS location).
- *Mixed Data Collection* is data collected through the combination of active and passive methods.

Finding: Finding is an umbrella term for an outcome or result from a research study, and can refer to one or more of the following (*adapted* from the Presidential Commission for the Study of Bioethical Issues 2013).

- *Primary Finding:* Researcher aims to discover A, and the result from a research study is relevant to A.
- *Secondary Finding:* Researcher aims to discover A, and also actively seeks D, a result known to be associated with the test or procedure, per expert recommendation.
- *Incidental Finding (anticipated):* Researcher aims to discover A, but learns B, where B is a result known to be associated with the test or procedures (including the data sources for digital phenotyping research) relevant to A at the time it takes place.
- *Incidental Finding (unanticipated):* Researcher aims to discover A, but learns C, where C is a result not anticipated to result from the test or procedure at the time it takes place.
- *Exploratory Finding:* Researcher aims to discover new findings, of unknown interest or significance, by employing a test or procedure designed to detect a broad array of results.

Result: A result, at the individual or group level, is “interpreted” data (see above for definition of “interpreted.”)

Individual Research Result: The term “Individual Research Result” (IRR) includes any “result” (as defined above—interpreted data) or “finding” (as defined above—primary, incidental, secondary, exploratory) about the individual research participant collected or generated by the research team as part of the research project. IRRs can be further sub-divided into the following categories.

- *Routine Results:* Results that are collected at baseline and regular study visits, such as weight, blood pressure, heart rate, blood results, and patient health questionnaire that do not require immediate follow-up. These may be standard of care testing and/or procedures that are conducted under the study protocol (MRCT Center 2017).
- *Informational Result:* Other environmental, financial, lifestyle or other health-related results about the individual participant that are not traditionally regarded as health or mental health data, but that might be informative, entertaining, or evocative (positive / negative) for a participant.
- *Urgent Results:* Results that may pose an immediate threat for the participant’s health if not treated or addressed (MRCT Center 2017).

Aggregate Research Results: The summary of group-level results from a research study.

Utility:

Clinical utility: The likelihood that an intervention (e.g., digital phenotyping tool) “can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful” to the research participant (*adapted* from (ACMG Board of Directors 2015)).

Personal utility: Data or results have personal utility if they “can be reasonably used by participants for personal decision making, actions, or self-understanding” (MRCT Center 2017; Botkin et al. 2018). We consider this term equivalent to “personal meaning” (Ravitsky and Wilfond 2006).

Validity: Adapting definitions from Botkin et al. (2018), MRCT Center (2017) and ACCE (Center for Disease Control 2010):

Analytical validity: The accuracy and reliability of a digital phenotyping tool to measure a predictor of symptom or illness (e.g., can the smart phone accurately and reliably measure number of hours slept, which might be used as a predictor in a model predicting onset of a manic episode). Analytical validity includes analytic sensitivity and specificity, and within- and between-laboratory precision.

Clinical validity: The accuracy and reliability of a digital phenotyping tool to detect or predict an outcome of interest (such as onset of mania) (Botkin et al. 2018). We consider this equivalent to what the FDA (2017) describes as “valid clinical association,” which is defined as “the extent to which the program’s output (concept, conclusion, measurements) is clinically accepted or well-founded (based on an established scientific framework or body of evidence) and corresponds accurately in the real world to the health care situation and condition identified.”

Return of Value: Adapting the definition proposed by Wilkins et al. (2019), return of value encompasses the “ways in which participants may perceive benefit from myriad types of information.” Return of value focuses on personal value (or “personal utility”) defined by the participants themselves, and thus requires engagement with participants, their caregivers, and their communities in the determination of value.

project. In some medical contexts, an interpretation might be synonymous with a diagnosis, e.g., processed data from an MRI indicates a subdural hematoma. But a result is not always a diagnosis, e.g., while a sudden change in sleep pattern may increase concern for mood or medication changes, it is not a diagnosis. As a nonclinical example, basic research utilizing personality assessments may reach a conclusion that someone is high in extraversion or openness or emotional stability, relative to the population. As these examples illustrate, interpreting data typically

involves correlation with other collected information outside the dataset (e.g., medical literature, pattern recognition) and/or implicit or explicit comparisons to population norms.

CONSIDERATIONS IN RETURNING IRRS IN DIGITAL PHENOTYPING IN PSYCHIATRY

Despite the growth of digital phenotyping research, and recognition that return of results should be addressed (Khodyakov et al. 2019; Wilkins et al.

2019), there has been no published guidance about return of IRRs in digital phenotyping research. In formulating such guidance, we start with the recognition that established guidelines for return of IRRs generally in biomedical research, and the emerging norm of returning results in participant-centered research, can meaningfully inform decision making by Institutional Review Boards, researchers, and participants. We ground our discussion here in the vignette presented at the outset, and utilize the terminology as defined in Table 1.

We note three aspects of digital phenotyping research that have implications for decisions about return of IRRs: (1) a very large number and various types of results could be returned, with much of the data collected passively and many results having the potential to affect participant behavior and health, or reveal socially stigmatized, politically sensitive, or legally relevant behavior; (2) great uncertainty about the actionability, analytical validity, clinical validity, personal utility of many of the results, including potential bias in the AI/ML systems being used to model the data and facilitate interpretation; and (3) significant risks to third parties from unintentional secondary collection of data from those third parties through the digital phenotyping tools.

Digital Phenotyping Tools Passively Collecting Large Amounts of Sensitive Data

Digital phenotyping research utilizes large amounts of data from multiple sources (Box 1). Moreover, much of these data will be collected passively. For example, as distinct from psychiatric research that requires participants to consciously engage with a researcher or research tool (e.g., participants are speaking to a researcher in an interview or completing a survey), in some digital phenotyping research, a single consent to have their electronic devices monitored could give researchers access to continuously gathered data such as: every website visited, image viewed, call made, text sent, physical location visited, and step taken. While the informed consent process would be a safeguard to ensure that participants agree to ongoing data collection, research suggests that after a period of adjustment, participants in digital phenotyping studies may revert to their normal behavioral patterns even though they are now being monitored (Mittelstadt 2017; Essén 2008; van Hoof et al. 2011).

It is not only the amount of data collected, but the *types* of data (and hence the types of results) involved that make return of IRRs challenging. Casting a net so

wide that it includes every text and email someone sends, and every physical location and every website someone visits, makes it more likely that those conducting phenotyping research may collect information that can create a revealing snapshot of certain behaviors and choices that may be socially stigmatized, politically sensitive, or have legal implications.

For example, the research team described in the opening vignette might learn if a person in recovery from addiction has purchased liquor, if symptoms of a mental disorder are manifesting, if a married participant is having sex in someone else's home, or if child pornography images are viewed. At the same time, the research team will learn potentially more innocuous details about their participants such as how many steps are taken each day, how participants are sleeping, and where participants like to hang out on the weekend. The research team might also be able to infer, in real time, rare medical events such as if the participant falls and is not able to move. A policy for the return of IRRs must thus be flexible to accommodate this broad range of IRRs that could be returned.

The policy for return of IRRs will also need to be cognizant of how the return of raw, processed, or interpreted data may affect participants. For instance, there is a deep literature on mental health stigma (Parcesepe and Cabassa 2013; Sickel, Seacat, and Nabors 2014), its serious consequences (Sharac et al. 2010), and efforts to reduce it (Yanos et al. 2015). To be clear, we do not describe here a research agenda for empirically assessing how return of IRRs affects participant behavior, e.g., how return of IRRs could serve as a psychiatric intervention or change behavior, though we view such a future research agenda to be valuable. We focus here instead on the current situation in which researchers need to develop policies on IRR despite the paucity of research on the impact that IRRs will have on those who receive them.

In the context of digital phenotyping research, a return of results approach should consider the dynamic relationship between public and personal stigma and self-stigma, and the results being returned. In the context of mental disorders, "personal" or "public" stigma is recognized as the attitudes that others have toward those thought to have a mental illness, while self-stigma is the individual's internalized perception of public stigma, both actual (that is, an accurate internal perception of the public stigma) and perceived (Vogel et al. 2013). These two types of stigma are interrelated (Latalova, Kamaradova, and Prasko 2014). Relevant to return of IRRs, the potential for exacerbating the impact of public stigma exists if

the returned data becomes known to others and contributes to negative attitudes about the individual receiving the results. For instance, imagine that a smart phone app sends an alert when a participant's data suggests that the participant may wish to see a mental health provider. If others, such as classmates or coworkers who regularly spend time with the participant, see or hear the alert, it could lead them to stigmatize the participant, and thus for the participant to be impacted by public stigma in this environment. Even if others don't actually stigmatize the participant, if a participant anticipates that they will or might, it could lead to increased self-stigma.

In addition, some of the results could expose an individual to criminal liability and other serious repercussions such as loss of employment. Digital phenotyping data can find, document, and preserve direct evidence of statutory violations, for instance being outside one's house after a city-imposed curfew, excessive speeding, and being a registered sex offender frequenting school playgrounds.

To illustrate, consider a situation where the research team infers that one of their participants is spending significant time at a bar drinking alcohol, and that on days when he drinks, he is much more likely to yell vulgarities at or threaten his family (measured through in-home sensors). The researchers could return results to this participant via smart phone on a daily, weekly, monthly basis, or even could program their system to send results in real-time. There are also many choices for how to communicate the result. For example, the participant could receive a notification indicating not only the purchase of alcohol but also the amount of time at the bar, as well as messages such as, "You are in the top 1% of all adults for number of hours spent drinking in a bar," or "It looks like you're going to the bar a lot. And on days when you go the bar, your behavior at home changes too. Please remember that consuming too much alcohol can lead to serious health problems." The research team could also communicate with the participant about resources that might be of interest. And of course, the research team could do nothing during the course of the study, but 2 years later, after the study has been published, send a full report discussing the (now 2 years old) behavior. The bottom line is that with so much sensitive data being collected, and so many ways to return results, the return of IRRs policy should address how it is anticipated participants may respond—and what, if any, responses the research team wishes to promote. Given the absence of research on the efficacy of these

various methods, we do not promote a particular method of returning IRRs as the preferred one *a priori*. As discussed below, we do recommend that an initial method be chosen prior to conducting the study, and then the return of IRRs approach should be reviewed at least annually. This balance of structure and flexibility is appropriate given how little is known about what effect return of IRRs will have on behavior and well-being.

Uncertainty About Analytical Validity, Clinical Validity, Actionability, Clinical Utility, and Personal Utility

Because digital phenotyping research is utilizing new combinations of data streams and novel analytical techniques on those data (e.g., automatic speech recognition in psychotherapy, Miner et al. 2020), there is likely to be much uncertainty about the analytical validity, clinical validity, actionability, and personal utility of the results. While genetic data now have benchmarks for reliability of the raw data itself (or the calls at least), there are no benchmarks for most digital phenotyping data streams, nor for the techniques that are assembling them. For instance, consider the opening vignette, where a research team may be able to infer when a participant has used, or is at risk of using, illicit drugs. This inference might arise from the participant's geographic location (e.g., first visiting an ATM and remaining there for the time it takes to withdraw cash, then visiting a location known for drug sales, sudden change in blood pressure and heart rate associated with heroin use, and text message activity consistent with a drug sale).

In order to make such an inference, the research team would need to ensure analytical validity of the relevant measures: the GPS device is accurately measuring the participant's GPS location, the heart rate and blood pressure measures are not fluctuating due to equipment malfunction or another cause, such as exercise; and that the measure of text message activity is reliably tracking actual text message usage. It is not hard to imagine challenges with analytical validity, e.g., the blood pressure measurement device gets jostled when the participant pedals a bicycle, so there is a higher blood pressure reading even though the participant's blood pressure has not actually changed.

Even with analytical validity, the results will not have clinical validity unless they can accurately and reliably detect or predict a relapse of heroin use. It could be that a certain combination of heart rate, movement patterns, and text messaging activity may

be indicative of a health concern. Or it could be indicative of nothing. Many digital phenotyping studies aim to establish correlation and predictive validity; returning IRRs in real-time may be premature.

Further complicating return of results are concerns regarding bias and fairness in models of behavioral interpretation and prediction. For example, racial bias has been identified in some widely-used health care algorithms (Obermeyer et al. 2019; Buolamwini and Gebru 2018; Goodman, Goel, and Cullen 2018), and concerns regarding bias and fairness are relevant to the data and analyses used for digital phenotyping (Martinez-Martin, Greely, and Cho 2021; Mulvenna et al. 2021). When datasets are not representative of the populations in which they will be used, which is common due to lack of diversity and representativeness in research enrollment, then the resulting tools may not be as useful, or could even be harmful, for the groups not represented in the research.

Digital phenotyping can utilize data streams that rely on linguistic interpretation (e.g., electronic health records, social media posts) or categorization of specific activity (e.g., video, movement), both of which may be more subject to misinterpretation or mislabeling, or simply missing data, for minoritized populations (Gianfrancesco et al. 2018; Haque, Milstein, and Fei-Fei 2020; Martinez-Martin, Greely, and Cho 2021). To date, little data is available on the representativeness of digital phenotyping samples, and this raises the question of what data should not be returned until and unless sufficiently representative samples are used, and when a sample is sufficiently representative across which demographics. To improve representativeness, the design and implementation of digital phenotyping data collection tools will need to take into account differences in how devices may be used in different communities. These differences can impact equitable data collection and analysis across diverse groups, such as race, gender, ethnicity, religion, socioeconomic or disability status.

In addition, the research team will still need to evaluate actionability. For instance, if the research team can accurately and reliably predict when a participant is at risk of using heroin, then the result would be actionable because there are certainly well-established treatment regimes for substance-use disorders, and knowledge of risk factors for relapse could guide participant decision-making, e.g., a participant might seek treatment for addressing the substance-use disorder or choose to act differently in order to mitigate risk of relapse.

But even if the results are not “clinically actionable,” they may be actionable if the result has personal utility for the participant. For instance, assume that the research team has established the analytical validity of its sleep measurements, GPS tracker, and measure of text message activity. Further assume that the research team has correlated location data and text messaging with a change in sleep patterns—when the participant visits a certain location and text volumes increase after 7 pm, they go to sleep later and wake up later—but have *not* yet been able to reliably connect these measures to risk of drug use. This result, showing a relationship between sleep patterns and text/GPS, might have personal utility for the participant because it improves the participant’s self-understanding of their daily rhythms and might also inform their future decision-making about how to optimize their sleep habits.

Guidance for return of IRRs in digital phenotyping will have to acknowledge this uncertainty concerning analytical validity, clinical validity, actionability, clinical utility, and personal utility, but it can consider existing guidance from related fields where uncertainty has been addressed. For instance, the American College of Medical Genetics and Genomics (ACMG) developed (Richards et al. 2008) and refined (Richards et al. 2015) guidance for the interpretation of sequence variants, acknowledging both the continuum of clinical significance from benign to pathogenic as well as the rapid evolution of understanding. This approach has been used by the ACMG to recommend whether and which genetic variants should be returned to participants and patients (ACMG Board of Directors 2012; Miller et al. 2021; Green et al. 2013).

As in other new fields, clinical validity and clinical utility are likely to increase over time. This suggests that research teams, in consultation with their IRBs, may need to consider updating return of IRRs protocol over the course of the study. For example, midway through a research study the research team may feel more confident that a certain pattern in the data is meaningful for predicting a health outcome. Accuracy and reliability of results will also vary by the level of analysis. For example, although historical weather patterns cannot tell us the exact day of a snowstorm, they can reliably tell us that, on average, winter will be colder than summer. Similarly, digital phenotyping data might be able to identify group-averaged patterns of heightened risk for relapse, even if those models are not predictive of a particular individual’s relapsing behavior.

A cross-cutting issue related to validity is the possibility that results were generated by an AI/ML system that was trained on data that were not sufficiently representative of the relevant characteristics of the participants in the present study. It is well recognized that non-representative training data may introduce biases into medical AI (Food and Drug Administration Center for Devices & Radiological Health 2021; Vokinger, Feuerriegel, and Kesselheim 2021). For return of IRRs, the question is whether it is a prerequisite for returning IRRs generated by AI is that the AI system must be trained on data that is inclusive of the populations being studied in the present research study. While such a bright line approach might prevent potentially biased results from being returned, it also could lead to inequities in return of IRRs because such a policy would prevent return of IRRs in studies with more diverse populations but allow return of IRRs in research with more homogeneous populations. To balance these concerns, we believe the best approach is to proceed with caution. In some instances, for example of high potential benefit to a participant, it may be ethical to return IRRs even if the results were generated by an AI/ML system with unknown representativeness or lack of representativeness in its training data. In this setting, however, the limits of predictability (or validity) and potential for bias should be explained to participants as part of the returned result.

We think this approach of cautious application while explaining limitations has a relevant precedent in sub-specialty medical care. In sub-specialty medical care, it is sometimes felt to be appropriate to cautiously apply information gained from one population (e.g., a general adult population) to guide the care of another target population (e.g., a geriatric population, or an adolescent population, or a population with rare health conditions) when the relevant information on the target population does not exist (as is often encountered in geriatric psychiatry or child psychiatry, for example).

Risk to Third Parties

Digital phenotyping research has the ability to collect highly sensitive information, not only from research participants but also from individuals who come into contact with the research participant. For instance, a study using Bluetooth proximity data might identify many others whose GPS could be correlated to a place of illegal drug use. Or a research participant might be included as a recipient on an email in which the

sender seems to be making a threat and has attached a photo of the sender with a stockpile of guns. In these hypothetical situations, the research team would be confronted with the challenge of what, if anything, to do with regard to third parties—those who may not have a connection to the research—implicated by the data being collected and possibly returned.

These effects on third parties are not unique to digital phenotyping research (as, for instance, genomics research reveals information about the subjects' parents and children, who may not have consented), and existing discourse from these related fields can be of use in developing policy for digital phenotyping researchers (Gordon and Koenig 2022). Effects on third parties should be incorporated into the risk/benefit calculus described in the next section.

FRAMEWORK FOR RETURNING IRRS IN DIGITAL PHENOTYPING RESEARCH

Recognizing the three features just described—many different data streams being collected, with potentially great uncertainty about validity/actionability/utility, and unanticipated impact on third parties—we propose a framework that is grounded in the core bioethics principles of balancing benefit/value vs. risk of returning the results/data, respect for persons (both participants and other third parties affected by return of the results), and promoting justice in returning data (The National Commission for the Protection of Human Subjects of and Biomedical and Behavioral Research 1979). Further, we adopt a practical ethics approach that allows for flexibility in application, emphasizing procedural justice, justification for the ethical choices made, and transparency in the decision-making process.

We recommend that decisions about the return of results be made on a study-by-study basis. A study-by-study approach is consistent with similar analyses (MRCT Center 2017; Botkin et al. 2018), and it requires documentation of choices made. In advance of study initiation, one first step is to identify whether the research will be subject to certain laws that can affect policies for returning results. Depending on the goals of the research and the types of data analysis to be performed, some studies may generate interpreted data/results or individual-specific findings that resemble diagnoses or predictions about the participants' physical or mental health. Returning such IRRs to participants could potentially trigger a need to obtain an Investigational Device Exemption from the U.S. Food and Drug Administration (or equivalent

| | | <i>Potential Risks to Participant</i> | | |
|--|------------------------|--|---|--|
| | | Low Risk | Unknown Risk | High Risk |
| <i>Potential Benefits to Participant</i> | High Benefit | [1] High benefit and low risk Default presumption: Offer <u>Return</u> of IRRs | [2] High benefit and unknown risk No default presumption | [3] High benefit and high risk No default presumption |
| | Unknown Benefit | [4] Unknown benefit and low risk No default presumption | [5] Unknown benefit and unknown risk No default presumption | [6] Unknown benefit and high risk Default presumption: Do <u>NOT</u> return IRRs |
| | Low Benefit | [7] Low benefit and low risk No default presumption | [8] Low benefit and unknown risk No default presumption | [9] Low benefit and high risk Default presumption: Do <u>NOT</u> return IRRs |

Figure 1. Framework for developing individual-specific return of results protocols in digital phenotyping research in psychiatry.

requirements for research performed in other nations) (Congress House of Representatives 2020a). Another concern is that some research is governed by privacy laws of the European Union, the United States, and some U.S. states that require individuals, upon request, to be granted access to certain types of data and results (“Sec. 13.04 MN Statutes - Rights of Subjects of Data” 2022, Subd. 3; U.S. Department of Health & Human Services 2020; The European Parliament and the Council of the European Union 2016; Social Security Administration 1974; “Assembly Bill No. 375 - Chapter 55 - Privacy: Personal Information: Businesses” 2018). These mandated access rights are conceptually distinct from return of results—they exist so people can assess the level of privacy risk they face from personal data stored by others—but they sometimes seem in conflict with ethical policies that IRRs should not be returned. When such laws apply to a research project, researchers are required by law to grant access to certain types of data upon request, and researchers, IRBs, or others cannot block or override such access (The Multi-Regional Clinical Trials (MRCT) Center 2023). Thus, a first step in developing a protocol on IRRs is to contact the responsible personnel at one’s institution to assess which laws apply to the research. At most institutions, this would mean contacting the general counsel’s office, the chief privacy officer (for HIPAA and

state privacy requirements), the human research protection program/IRB, and/or the regulatory affairs office (for FDA-related questions).

In the absence of legal or regulatory directives requiring individual access to data, returning IRRs appears to be consistent with participant expectations, especially when IRRs are clinically and/or personally actionable, and with emerging best practices and regulations (Botkin et al. 2018; Secretary’s Advisory Committee on Human Research Protections 2015). In collaboration with the IRB regarding local norms and context, research teams should discuss and decide whether, and how, each stream of individual data, as well as key analyses of those streams, will be returned (or not) to research participants, and then communicate, with justification, that decision to the IRB. The IRB-approved decisions on return of results should then be clearly communicated to participants as part of obtaining informed consent (Presidential Commission for the Study of Bioethical Issues 2013).

To facilitate development of study-by-study decisions about returning IRRs in psychiatric digital phenotyping research, we propose a 3×3 benefit-harm framework to contrast low, high, and unknown benefits of returning data versus low, high, and unknown risk of harm to participants (Figure 1).

The balance between potential benefits and risks varies by the type of data stream being collected.

While both benefits and risk are continuous variables, along a spectrum, our framework operationalizes the concept into a 3×3 matrix of “high,” “low,” and “unknown” potential benefit/risk. To place a data stream into a cell requires two initial steps: (1) assessing potential benefit as high, low, or unknown; and (2) assessing potential risk as high, low, or unknown. We use the term “benefit” to capture the many dimensions of “utility” and “value” captured in Table 1.

We use the term “unknown” to describe a wide array of situations in which there is insufficient information (e.g., on accuracy, reliability, validity, utility, safety, etc.) to adequately assess benefit or risk. We recommend presumptive default rules for each of the cells in this matrix. We also show how this framing can be used to consider issues such as equity, e.g., by determining if returning IRRs will systematically harm/benefit certain groups of participants more than others; resource capacity, e.g., if the research team has the requisite resources to implement any promised return; and parentalism, e.g., if the research team underestimates the capabilities of the participants in understanding and acting on certain results.

For research conducted at sites governed by privacy laws that grant individual rights of access to certain types of data (e.g., the HIPAA Privacy Rule and GDPR), it may not be possible to refuse to return IRRs, if the individual requests access. The HIPAA Privacy Rule provides a narrow exception allowing researchers to suspend individuals’ access to data and results from clinical research studies temporarily while the research is in progress (Office of Federal Register 2023, (a)(2)(iii)). To take advantage of this exception, researchers would need to obtain participants’ consent to the suspension of their access rights at the very outset of the study, as part of participants’ consent to the research. Moreover, access must be reinstated as soon as the research is completed, so this exception defers access only temporarily (Office of Federal Register 2023, (a)(2)(iii)). Unless these preparatory steps are taken at the start of the study, this exception does not apply, and individuals have a right to request access to their data and IRRs held in designated record sets at HIPAA-covered research sites.

When confronted with an individual access request, HIPAA-regulated researchers “may not impose unreasonable measures on an individual requesting access that serve as a barrier to or unreasonably delay the individual from obtaining access” (U.S. Department of Health & Human Services 2020). It would violate the law for researchers, IRBs, or counselors to try to

discourage participants from exercising their lawful access rights. Researchers and IRBs can, however, help protect participants and address ethical concerns by preparing “point of data delivery (PODD)” disclosures, which are standard warnings and disclosures that will accompany data and IRRs at the time researchers respond to HIPAA access requests (Tayeh et al. 2022). These PODD disclosures could include, for example, disclosing any data-quality concerns and uncertainties about the analytical validity, clinical validity, and clinical utility of the data; warnings against misuse of the data—for example, a warning not to base medical decisions on the data without consulting their health care professional; disclosing that the information is being provided strictly to comply with privacy law and is not intended for medical decision-making; and warning recipients to protect their own privacy by making responsible decisions about any further sharing of the data they receive (for example, by checking privacy policies before contributing the data to a citizen science research project) (Tayeh et al. 2022).

Spurring Dialogue on Return of Results: Who, What, Where, When, How?

The framework encourages dialogue around the following: *Who* will receive results from the research team (e.g., how might the participant’s culture and race, ethnicity, age, sex, gender, culture, disability, and socioeconomic class affect decisions about returning results); *What* will be returned (e.g., raw data, processed data, interpreted data); *Where* the data is being sent (e.g., in what location and with whom will the participant be when receiving the results and what local/state/country regulations are implicated by that geographic location), *When* (and how frequently) the data will be returned (e.g., once at the end of the research project; at intervals such as daily, monthly, hourly; in real time); and *How* the data will be returned (e.g., on the participant’s smart phone app, in an electronic health record, verbally through a phone call or meeting with researchers or clinicians). Implied in the framework is the overarching question of “Whether” to return data at all, since applying the framework, and considering the who/what/where/-when/how, may result in a decision not to return a data stream.

At the core of the framework lies a challenge that can only be resolved on a study-by-study, and data-by-data basis: determining the return-worthiness of the data. That is: by what metrics and criteria should

“benefit” and “risk” be evaluated? We encourage approaches that include research participants in the evaluation of potential benefits and potential risks (Wilkins et al. 2019). Participants and researchers may vary in their preferences related to return of results (Lázaro-Muñoz, Torgerson, and Pereira 2021) and, whenever possible, participants should be given options for which data to receive, and even when to receive it (e.g., notify me when I’ve had over 3 h of screen time in a single day.)

Research teams will need to ensure that they have the resources to deliver on promised return of results policies. We envision that resource availability determinations would be independent of the initial risk/benefit calculus. That is, the research team should identify the IRRs they wish to return, estimate the resources required to return these IRRs, and build that into the study design and if applicable, request for funding. If researchers do not have adequate resources to conduct all of the return of IRRs they aspire to, the protocol should reflect current ability to return IRRs. Revision of the IRR protocol can expand scope if additional resources are secured. Resource availability may mitigate the risk or augment the benefit of returning a particular result (e.g., if return was done by a specialized provider, or came with access to particular health or personal resources), but this should be thought of as separate from the initial risk/benefit calculus of the IRR in question.

Research teams will also need to remain vigilant in *revising* initial risk/benefit calculations as the research progresses, and especially as research findings lead to improvements in validity and utility of results. Revision of risk/benefit analysis is also vital for dealing with unanticipated incidental findings (IFs). While anticipated IFs can be factored into the initial protocol, by definition the protocol cannot account for unanticipated IFs. We recommend that the return of IRRs approach be reviewed and revised at least annually.

Who? There is significant heterogeneity in participants both across and within digital phenotyping studies. Thus, we encourage an approach to return of results that is sensitive to the backgrounds, values, priorities, cultures, and lived experience of those participants. Factors relevant to return of results might include race, ethnicity, gender, culture, disability, and socioeconomic class. For instance, in the context of genetic counseling, significant concerns have been raised about ELSI issues in implementing genetic counseling services and returning genomic research results in diverse communities (Raymond et al. 2021;

Young et al. 2021) and low-resource countries (Holzer et al. 2021; Zhong et al. 2021).

Research on genetic counseling and in the context of returning results in genomic studies has found a need for culturally-informed counseling (Burnett-Hartman et al. 2020; Young et al. 2021; Fehniger et al. 2013). At present there is no analogous field of “digital phenotyping counseling” and little guidance on which aspects of digital phenotyping results may be most culturally sensitive. But research in genomics return of results would imply that a one-size-fits-all approach to returning results in digital phenotyping research would overlook important variations in value/culture in the populations to whom results are being returned. In digital phenotyping research, researchers might need to consider whether certain data streams have the potential to generate stigma in particular cultures.

What? Deciding what to return involves related decisions about which types and combinations of data to return—raw data, processed data, and interpreted data. If research participants are simply given raw data, it may not be user-friendly and equity concerns may arise if processing that data requires specific expertise or an out-of-pocket expense to pay a third-party data analyst service. For example, in genomics research the “BAM file” (a specialized file format containing sequence info) could be returned as raw data to participants. However, this file type requires special knowledge to learn how to open, let alone analyze oneself. One may need graduate training in genetics or to hire someone with that training to access and interpret the data. Similar phenomena could be encountered depending on the format of the data returned in digital phenotyping. Of course, users may have the requisite abilities to manage such data and may desire it even if they don’t. For example, one review of the literature on this issue found that participants frequently want access to raw data such as BAM files, even though researchers worry about the usability of it (Wright et al. 2017). Researchers in digital phenotyping will need to balance concerns regarding how such data might be reasonably returned with considerations of benefits such as “autonomy, empowerment, health prevention, reciprocity, and improved trust” (Wright et al. 2017).

Interpreted and processed data, including data patterns and predictive data, might lead to recommendations to seek medical care. The granularity of the data, as well as the comparisons that are presented (e.g., compared to others in the study, compared to a normed sample), will likely affect both utility and

risks. Of particular note is that a large number of data streams combined with powerful analytic methods means that researchers will have many ways of analyzing, presenting, and thus returning data and results. Our framework does not presume that data processing that is conducted by a human is *prima-facie* preferable from a risk/benefit perspective than that done by an AI/ML system if the result and IRR is otherwise the same. That is, in some cases data processed by AI/ML models may provide greater analytic or clinical validity than data that does not employ such methods. In other cases, use of AI/ML may be riskier or less beneficial because the models may be biased.

A prerequisite to successful digital phenotyping is the consistent and reliable collection of data in real time (Nebeker, Bartlett Ellis, and Torous 2020; Torous et al. 2019), and increasingly “the main intellectual challenge in smartphone-based digital phenotyping has arguably moved from data collection to data analysis” (Onnela 2021, 50). Advances in data analysis will provide an even more complex menu of options for returning IRRs. While the traditional distinctions between “raw data,” “processed data,” and “interpreted data” are still useful, researchers will be faced with decisions about which *combinations* of raw, processed, and interpreted data streams to return.

Participants may also be able to take their raw data to other vendors and have it processed and interpreted, as is possible with genetics data, which allows them to seek second opinions and have the data re-analyzed as technology improves. For example, a polygenic risk calculator may not have existed for a certain disease at the initial time of the participant’s sequencing, but if it emerges later a participant could run their raw data through the new pipeline.

When? Much existing guidance on returning IRRs conceptualizes the timing of return at either the end of a study, or perhaps at a few critical moments while the study is underway. By contrast, many of the data collected in digital phenotyping research can be more easily returned in real time, at researcher-specified intervals or at a moment triggered by an algorithm. For instance, participants could receive daily reports on their sleep data, hourly data on their step counts, or minute by minute data on heart rate and screen usage (Reeves, Robinson, and Ram 2020; Reeves et al. 2021). Thus, return of results in digital health research could be a *continuous process* and not a singular event. Thresholds, informed by participant preference, could also be incorporated. For instance, a user could choose to receive heart rate data only when it went below 50 or above 140 beats per minute.

When a threshold is reached and a result is returned immediately, there may not be time in that moment for contemplation or consultation. In such instance, the threshold value or calculation needs to be pre-defined, and effectively communicated to all involved, potentially including participants, those they live with (e.g., since in certain cases and certain alerts, law enforcement might be involved), outpatient clinical team members, study doctors, and the IRB or other institutional bodies.

It should also be noted that for those data that do require confirmatory testing or analysis, a lag between knowledge of a result and returning that result (i.e., only after sufficient further analysis is conducted) can produce anxiety in both participant and researcher. Just because more alerts can be sent, however, does not mean they should. “Alarm fatigue” is a challenge for clinicians (Sendelbach and Funk 2013), and participants who receive too many alerts may learn to ignore them.

As the possibility of real-time interventions and the ability to automate return of data increase, timing may be particularly challenging. For instance, if there is a small window for an IRR intervention (e.g., send the warning message *now* and not 2 h from now), with little time for extensive consultation, then thresholds for return and associated protocols need to be pre-defined and outlined in detail to all stakeholders, e.g., patient participants, outpatient clinical team members, study doctors, and the IRB or other institutional bodies.

Where and How? A unique aspect of return of IRRs in digital phenotyping research is that the smart phone or other device platform for data collection is also a potential platform for return of IRRs. Researchers might also send results to an electronic health record, send a secure email, or mail a hard copy letter. There are differing privacy concerns with each modality. Many health systems have made their electronic health records immediately accessible to patients via electronic gateways, so researchers could conceivably leverage that existing infrastructure to facilitate timely IRRs. Yet the return of data to smart phones must account for the possibility that the participant could conceivably be in any state or country, potentially implicating that jurisdiction’s law, concerns around remote research more generally (Gelinis et al. 2021), and data policies of the phone manufacturer and service carrier or internet service provider. In addition, the smart phone may not be in the possession of the participant, as when parents give their phone to a child to watch a video or when a group of

friends are making a group video call. In such situations, even an alert (such as “New results from the hospital research study”) could be information that the participant does not want others to see. Researchers will thus need to consider privacy settings and methods of communicating that ensure the participant is the one receiving the information.

Utility and risk are also related to how the results are returned. For instance, will participants simply receive a text message alert with a link to a lengthy report, or will they receive a phone call from an expert who can explain the results (including, for instance, whether the results have clinical validity or not) and answer questions from the participant? Will any of the IRRs be returned automatically, with only a computer and AI/ML algorithm analyzing them? In which instances will a clinical consult be utilized? Visualization is also important and dovetails with the question of what is being returned. For instance, a smart phone alert that reads “IMPORTANT!” is likely to be understood differently than a lengthy email that conveys the same underlying information. The language used in returning results could also have an effect, positive or negative, on participant behavior.

Balancing Risks and Benefits

Dialogue concerning the Who, What, Where, When, How of returning results will help researchers determine into what risk/benefit cell a particular result fits. For example, when a result is returned will affect its benefits and risks. To illustrate, consider an alert that—if returned before a participant relapses into self-harm behavior—could potentially prevent the self-harm by helping the participant seek out support. The potential benefit of such an alert is very high, but only if returned in time to prevent the harmful event. To take another example, if results are returned in a language that is not well understood by the participant (or in a form that requires substantial additional analysis or interpretation), its benefit will be reduced—and risk might increase because the likelihood of misunderstanding rises.

These determinations should include assessment of risks and benefits to third parties, as discussed above. Also relevant to these determinations is the availability of the data stream to participants outside of the research protocol. For example, many apps allow users to generate daily sleep quality reports, so there may be low *relative* benefit from return of sleep quality data from the research team. We anticipate that where the greatest benefits will accrue is from the integration

of multiple streams, typically not available via commercial apps, that generate additional insights (and perhaps hold greater risk) for participants.

The default presumption is to offer the return of data for data streams in the *high benefit and low risk category* (Cell 1). Of course, some type of benefit has to be sufficiently documented before cell 1 is relevant. An example would be returning step count data and exercise activity data. With regard to benefit, there is evidence from the consumer market that individuals often like to track this data. This suggests that participants would derive value from having these data, and with regard to risk, individuals learning of their step counts might be deemed low risk. Returning nighttime inactivity data (as a proxy for sleep) is already done in the consumer market and could be another example of high benefit and low risk; if, however, the study involved people with prominent anxiety about insomnia or bipolar disorder (where sleep patterns are clinically significant), then this same data might become high benefit and unknown risk. By contrast, for data streams in the *low benefit and high risk category* (Cell 9) the default presumption is *not* to return IRRs. An example would be providing the participant with a message that they should seek out a clinician because they may be at risk of developing a neurodegenerative disease based on an analytic method that has not been validated. Here, the benefit could be low because the data is more noise than signal. The risk could be high because the participant might experience stress and might even pursue medical treatment that would not be warranted. For the same reason, the presumption is *not* to return data in the *unknown benefit and high risk category* (Cell 6).

For the remaining six cells in the table, including all those with unknown risk, we do not offer a default presumption. Where the cell notes that there is no default presumption, the research team should weigh the benefits and risks and determine (for each data stream, as well as combinations of data streams) whether data will be returned. For example, the *high benefit and high risk category* (Cell 3) might include results (such as statistical markers) that suggest the likely onset of a psychotic break. The data could contribute to prevention of the psychotic break or earlier intervention for support or treatment. On the other hand, returning the data could lead to stigma and distress—including unnecessary distress if the prediction turns out incorrect—so it is also high risk. There is also no default presumption for data in the *low benefit and low risk category* (Cell 7). An example would be raw data such as the amount of data transferred on a

cell phone in a month that has few privacy concerns, but also limited benefit. Finally, an example of an unknown benefit, unknown risk could be the detection of periods of pauses in respirations at night in a study with a wearable device when there is uncertainty about whether this is a technical artifact of the device or true apneic events that could signal the incidental finding of sleep apnea.

As these examples make clear, there are both opportunities and challenges of returning IRRs. For instance, returning participant data may be part of developing more “rigorous, inclusive, and representative” behavioral research in psychiatry (Germine et al. 2021). A further plausible, yet unknown, benefit or risk of returning IRRs is that the participant’s behavior and/or mental state may change. For instance, if researchers are collecting sleep data, perhaps returning daily sleep report data will allow participants to develop better sleep habits. Such outcomes are unknown at present.

Additional benefits may include improved data transparency if returning data—especially data that are collected passively—leads to a better understanding of what data are being collected and how they are being used, and better retention in the study (if participants feel more engaged). To the extent that returning data is part of a broader effort to further participatory research in science, it can also be a recruitment tool as “participation in research is incentivized by the desire to contribute to science, insight into the research question being studied, as well as return of study data and individual research results” (Germine et al. 2021, 5). Relatedly, an additional benefit of returning data may be enhanced trust between the research team and participants. Trust is particularly important because digital phenotyping relies on technological intermediaries that may be suspect due to privacy concerns (Brown 2020). Returning data might also increase comprehension of the study since research participants will have a better understanding of what data, including sensitive data, have been collected.

A drawback of returning IRRs is the potential to produce negative effects on behavior and mental states. As discussed above, there is a lack of knowledge about when processed data have been sufficiently validated to justify return, and how returning results will affect participant behavior. One related concern is the lack of “digital phenotyping counselors,” in contrast to genetic counselors who are well established, with dedicated journals, graduate programs, and a professional society. Genetic

counselors play a vital role in the return of genetics results. But there are simply no parallel counselors to help participants understand their digital phenotyping results. Privacy concerns also emerge with regard to how the data is shared and with whom. As with return of results in other biomedical research, there may also be confusion of research participation with clinical care, uncertainty about whether digital phenotyping results are entered into the medical record, and participant apprehension, as returned results may raise more questions and distress than they resolve.

How to navigate these many challenges will necessarily require consideration of practical constraints, such as the research team’s resources and the logistics of returning results. Our recommendations for digital phenotyping research in psychiatry are generally consistent with previous guidance on return of results, including the recommendation that whenever participants are offered the opportunity to receive data, it should be the participants’ choice as to whether to do so (The Multi-Regional Clinical Trials (MRCT) Center 2023, 2017; Botkin et al. 2018).

Applying this framework will be context-specific and many important issues deserve further attention. These include: informed consent; legal issues such as who controls access to data, and the applicability of HIPAA and CLIA for various data streams; ethical issues with AI digital phenotyping research, such as whether AI results are biased and thus inaccurate for some population subgroups, and/or whether findings from AI systems are transparent and understandable to researchers, care providers, and the people whose data were processed; post-study obligations to individual participants and to the community; appropriate data storage and sharing in ways that protect privacy; ethical obligations, if any, to re-analyze data periodically; policies on participants’ ability to opt-out of receiving IRRs, opt-out from secondary uses for their data, or revoke consent after a study has begun and have their data removed from the study; return of aggregate group results; incidental findings in the context of these new types of data streams; the potential sharing of results with others beyond the participant (such as clinicians and law enforcement); sharing of data with other researchers; returning results in international research contexts; and obligations to submit programs to regulators, such as the U.S. Food and Drug Administration (FDA), for review prior to commercialization.

Nor did our analysis explore in depth the issue of the conditions under which reporting of results to a third party or to the participants themselves may be

mandated or prohibited by law, ethics, or institutional policy. For instance, if a research team is collecting screenomics data (Reeves et al. 2021) and a participant's screen shows engagement with a child pornography website, the researchers may be under obligation to report.

Partnerships with private firms and third parties for data collection and analysis further complicate the analysis. For instance, rather than generate their own datasets a research team may be granted access to digital phenotyping data already collected from a company's users. Such arrangements would create a large lag between the moment of data collection and the moment of data analysis, with implications for real-time versus retrospective return of results.

Updating Return of Results Policies as Research Emerges

An important goal for digital phenotyping research is to study return of results *as an intervention*. A promise of digital phenotyping research is that it can positively change the trajectory of behavior, from encouraging someone to get more exercise to reducing self-harm and antisocial behavior. For example, multiple research teams are attempting to use in-app interventions to improve college student mental health (Melcher, Hays, and Torous 2020), and to prevent relapse in schizophrenia (Rodriguez-Villa et al. 2021). In such studies, in order to assess the effect of returning results, study design may require that different groups of participants receive results at different times, in different ways, or not at all. An ethical framework should distinguish between return of results offered during the study as a study intervention and return of results that are not part of a study intervention.

The approach we propose allows for significant flexibility for researchers, clinicians, IRB members, sponsors, and participants in using these new research findings to update whether, what, and how data should be returned in digital health research in psychiatry. More specific guidance and applied decision-making tools for specific types of digital phenotyping research will require further research.

At present, however, the analytical validity, clinical validity, actionability, clinical utility, and personal utility for many digital data streams are unknown, and there is minimal empirical evidence to know whether and how return of IRRs (or the withholding of IRRs) will affect the behavior and mental states of those who receive the information. Digital phenotyping

research designs presently include many exploratory and hypothesis-generating studies, and the data streams are expanding (e.g., incorporating data from smart shoe sensors, car sensors, and in-home appliance sensors). Return of results guidance must thus be flexible to account for the continuous expansion of data and data sources.

For some research data streams—such as MRI brain scans (Shoemaker et al. 2016)—there is existing guidance related to returning IRRs. But even these more established guidelines may require revision as collected data may not be reviewed by humans in a way that makes it compatible with mandated reporting guidance or timely return of results. Some digital phenotyping data may be reviewed soon after they are collected, but other data may be reviewed months or years later. Participants should be informed about the anticipated types of timing of data analysis during the consent process.

We clarify that it is beyond our scope in this article to provide detailed analysis of the return of results to third parties, for instance which results will be returned for medical, clinical, or legal reasons. Future work can consider whether and when researchers should share or offer to share data with a third party designated by the participant (e.g., spouse, therapist, psychiatrist), or an unaffiliated third party (e.g., emergency services or employers). Also beyond the scope of this article is a more extensive legal analysis of pertinent regulations, federal and state laws, and institutional policies related to mandatory reporting, duty to warn, and the like. But we note that researchers should be aware of participants' federal right of access to the contents of their "designated record set" (DRS) held by any HIPAA-covered entity (Wolf and Evans 2018). In addition, participants should be informed of mandated reporting that might be implicated by the research study. For instance, in 11 states, faculty and staff at higher education institutions are required to report instances of child abuse and neglect under certain conditions, and healthcare professionals are mandatory reporters of child abuse in 47 states (Congress House of Representatives 2020b, (b)(2)(B)(i)).

Applying Framework to Illustrative Hypothetical Case

We opened this article with an illustrative hypothetical to motivate our analysis, and we return to that hypothetical case here to apply our proposed framework. The hypothetical research team aims to understand the factors that increase or decrease the likelihood of

symptoms of severe mental illness in youth, paving the way for more effective interventions. Our framework makes clear that it is of paramount importance that the research team initially develop its return of IRRs approach *before the research begins*. The approach should then be revisited, and if needed revised, as the research progresses.

In initial development of the return of IRRs plan, our framework suggests that the research team should think carefully about who their participants will be, and to avoid parentalism by not underestimating the capabilities of those participants in understanding and acting on certain results. This could be accomplished by talking with potential participants and patient advocates during the research design phase. This is consistent with our recommendation that researchers include participants in the evaluation of potential benefits and potential risks. The team should also assess its resources to implement any promised return of IRRs and discuss with current and potential funders.

While a more detailed vignette would be required to formulate a specific plan, we can consider the outline of what such a plan should entail. *Who*: the participants in this study are potentially vulnerable and marginalized youth—young people with mental illness. If the youth are minors, parents and legal guardians will also need to be consulted. It is well recognized that access to mental health services is scarce, and thus the research team should factor that in its return protocol, for instance clarifying that these are research not clinical results and sharing resources for further care along with results. *What*: the data being collected is broad and deep, allowing for sensitive inferences about participants use of illicit drugs, sexual activity, liquor purchases, driving while drunk, visiting pornography websites, and having suicidal ideation. Returning data streams that could allow for such inferences falls into the High Risk category, and this data should only be returned if there is high benefit to participants. More details would be needed to determine high benefit but conceivably a return of IRRs that mitigated the risk of drug use relapse, severe psychiatric decompensation (e.g., hyper-sexuality in a severe manic episode), or self-harm behavior could qualify. While the high-risk data should only be returned where the benefit is high, other data streams may be low-risk. For example, daily measures of sleep may be of low or unknown risk and may provide benefit if it helps the participant improve sleep quality or seek closer follow-up with established providers (e.g., if the person already knows that insomnia is one of their early indicators of a possible manic or

hypomanic episode). It is worth emphasizing, as we do above, that the researchers here will be faced with decisions about which *combinations* of raw, processed, and interpreted data streams to return.

When: The hypothetical assumes that the digital phenotyping technology being used in this research project has adequate resources to facilitate return of individualized results to each participant, on a monthly, weekly, daily, or even more frequent interval. Intervals for return of IRRs should be aligned with estimated benefit and risk. A sleep quality report, for instance, might be returned daily. An example of real-time feedback might be positive reinforcement related to activity data, e.g., an alert sent immediately after the wearable device detects exercise. Real-time return of IRRs may also be warranted in the high-benefit/high-risk situations described above, e.g., to avoid relapse or self-harm.

Where and How: Although the data is being largely collected by technology and could be returned with messages in apps and on devices, the research team should think carefully about where it will need humans to return IRRs. In this research, where participants are youth with mental illness, the research team should consider engaging professionals with expertise in working with youth to facilitate return of IRRs. If the research study is geographically dispersed, then these conversations with participants may need to occur via video or telephone, rather than in-person.

Providing clarity on where to start with an individual study: Even without more details other than the vignette description, our framework demonstrates its utility in outlining core aspects of a return of IRRs plan for an individual digital phenotyping study. With these core aspects in place, the return of IRRs plan can be further developed as the details of the research design are considered and refined.

CONCLUSION

This article provides a framework to address a critical unmet need: guidance for returning results in rapidly expanding research in psychiatry using digital phenotyping tools.

The framework can serve as a practical foundation on which to explore the many unanswered questions surrounding returning IRRs in digital phenotyping research in psychiatry. Future dialogue and research should include a diverse and expanded group of stakeholders; indeed, stakeholder input into the question of returning results is of heightened importance when research is being conducted in vulnerable and marginalized populations. Relatedly, returning IRRs requires

time and resources, and research teams must be able to deliver on what they promise participants with respect to returning data. Empirical research, especially research with those most likely to be affected by return of IRR policies, is needed on the question of what participants *want* in terms of return of results and how returning particular types of results will affect individual and group behavior.

In the absence of such empirical data and given the likelihood of significant variation in analytical validity, clinical validity, actionability, and personal utility across emerging digital phenotyping tools, we recommend that research teams balance the interests discussed in this article. There will be instances in which the return of IRRs poses little risk and could generate significant personal benefit for participants. In such cases, participants should be given the option to receive IRRs. Where the benefits and risks are unknown, the judgment is more difficult. But as digital phenotyping tools improve, we anticipate more research in which return of IRRs could provide benefits to participants. Thus, it is imperative that all digital phenotyping research teams begin preparing now to address the Who, What, Where, When, and How of returning IRRs in their research programs.

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