Reporting incidental findings from non-biological assessments in human subject research

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Abstract
Incidental findings in research with human participants may have implications for a person’s present health or future health outcomes. Current guidelines focus on methods for handling and reporting incidental findings from biological test data but incidental findings might also arise from non-biological tests. This article presents three examples in which the results from non-biological test data can be predictive of future disease and should be disclosed to research participants. It is intended to increase awareness and facilitate further discussion about the reporting of incidental findings from non-biological data.

Keywords
Incidental findings, results in reporting, research ethics, non-biological incidental findings

Within the scientific community, the reporting of incidental findings arising from validated test data to clinical research participants is widely accepted as an ethical standard. Incidental findings are defined by the American Psychological Association (APA) as “observations of potential clinical significance unexpectedly discovered in

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research participants and unrelated to the purpose or variables of the study” (APA, 2011). In other words, incidental findings have possible implications for the present and/or future health and wellbeing of the participant. It should be noted that some definitions of incidental findings set forth by U.S. governmental and professional research organizations do not include potential clinical significance as a defining trait. Furthermore, it must be considered that some definitions of incidental findings, such as one provided by the Presidential Commission for the Study of Bioethical Issues (2016), describe incidental findings as arising from the use of a test or procedure outside of its original purpose. Other organizations, such as the APA (2011) and the U.S. Department of Health & Human Services (2017), define incidental findings more broadly as findings unrelated to the aims of the study. In accordance with the latter, Wolf (2013: 559) defines an incidental finding as “a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research but is beyond the aims of the study” and claims that incidental findings may arise during initial screening for participant eligibility and collection of baseline data. In this paper we adopt the definitions set forth by APA (2011) and Wolf (2013: 559) for our discussion of incidental findings. That is, we define incidental findings as unexpected findings arising in research that are unrelated to the objectives of the study, and have potential clinical significance related to the individual participant’s health or well-being.

The practice of informing medical and behavioral research participants of health-related findings has only been relatively recently established as a standard in the field of research. The mid-20th century Tuskegee Syphilis Study (McCallum et al., 2006; Rothman, 1982) and Willowbrook Hepatitis Experiments (Rothman, 1982) serve as extreme examples of the dangers of exploiting participants in clinical research and highlight the ethical responsibility of researchers to inform participants of procedures and risks of a study, as well as to disclose potentially important health findings resulting from their participation. Although there is currently no legislation in the U.S. pertaining to the reporting incidental findings, some governmental and professional research organizations have published guidelines for doing so. This guidance is predominantly focused on incidental findings arising from biological test data, with limited recommendations for researchers and institutional review boards (IRBs)\(^1\) to consider incidental findings arising from non-biological test data. The Presidential Commission for the Study of Bioethical Issues (2016) includes only genetic sequencing, testing of biological specimens, and imaging in their discussion of incidental and secondary findings. The American College of Medical Genetics and Genomics (AMCG) has published a list of specific genetic anomalies that they strongly suggest reporting to participants, as they indicate increased risk for disease (Kalia et al., 2017). Similarly, the American College of Radiology (ACR) Incidental Findings Committee offers specific recommendations for dealing with mediastinal and cardiovascular incidental
findings (Munden et al., 2018). The U.S. Department of Health & Human Services (HHS) (2017) guidelines for reporting incidental findings focus on abnormalities in X-ray, MRI, and genetic data; incidental findings arising from social behavioral research and other fields of research are acknowledged, but it is claimed that these implications are not directly related to medical care. The APA is the only organization that we found to have published an online discussion of incidental findings arising from non-biological test data, such as low memory scores in participants in the control group of cognitive research, or unexpected findings of symptoms of a psychiatric condition in mental health research questionnaires (APA, 2011). The APA recommends that investigators carefully consider the potential for incidental findings in their research, and proactively create a plan for reporting these findings to participants (APA, 2011).

The purpose of this article is to propose that researchers, IRB members, and research ethics policymakers consider and evaluate whether non-biological test data that reveals unexpected disease or disease risk, that is unrelated to the primary purpose or outcome of the study, should be considered an incidental finding and communicated to participants. To support our assertion that non-biological test data should be assessed or evaluated with regard to returning valid health-related information, we provide three examples of circumstances in which non-biological test data can (1) return results that are based on a validated assessment process, (2) return results that have implications for the future well-being of research participants, and (3) return results which can be acted upon to limit, prevent, or decrease the risk of negative health consequences. The following three examples of validated non-biological tests meet the aforementioned three criteria for returning health-related information and thus may produce incidental findings in a research context as previously defined.

**Example 1: Autism screening checklist (M-CHAT)**

On average, children are diagnosed with autism spectrum disorders (ASD) at 4 years of age or later, despite parents’ first reports of concerns being made around 17–18 months (Kleinman et al., 2008). The Modified Checklist for Autism in Toddlers (M-CHAT) (Robins et al., 2009) is a 23-item questionnaire designed to screen children for early signs of ASD and developmental delays. This questionnaire assesses parents’ or guardians’ reports of the child’s social and emotional development, language and motor abilities, sensory responsiveness, and other early indicators of ASD.

There is robust support for the M-CHAT’s predictive value for early signs and later diagnosis of autism spectrum disorders and related developmental disorders in children several years before the average age of diagnosis (Chlebowskí et al., 2013; Pandey et al., 2008; Robins et al., 2014). Validation studies of the instrument have evidenced its ability to detect current diagnosable ASD and/or developmental
disorders (Chlebowski et al., 2013; Pandey et al., 2008) in children as young as 16 months as well as predict the onset of ASD several years after a baseline M-CHAT assessment (Kleinman et al., 2008). The instrument has also shown good test-retest reliability and predictive value in both children considered low- and high-risk for ASD and related developmental disorders (Robins et al., 2001, 2014).

Early intervention services, occurring as early as 2–3 years of age, have been shown to improve a child’s prognosis for autism spectrum disorders and other developmental delays (National Institutes of Health, n.d.). Behavioral therapies, such as Positive Behavioral and Support (PBS) and Pivotal Response Training (PRT), and social skills training may improve communication skills as well as correct maladaptive behaviors (National Institutes of Health, n.d., n.d.). The Mayo Clinic cites several treatment options proven to aid expansion of a child’s language, social, and behavioral skills (Mayo Clinic, 2018). In addition, medications such as SSRIs and nutritional therapy may be effective as part of a treatment protocol for autism spectrum disorders (National Institutes of Health, n.d., n.d.).

Given that the M-CHAT is a psychometrically sound instrument capable of detecting early signs and risk of autism spectrum disorders and related developmental disorders, and that interventions can substantially reduce the risk or severity of these diseases, research findings from the M-CHAT that indicate elevated risk should be returned to the child’s family. Having access to these findings allows the family to seek out early intervention services that may limit the development or lessen the severity of the child’s autism spectrum disorder or developmental disorders.

Example 2: Type 2 diabetes risk assessment (AUSDRISK)

Type 2 diabetes is a widely prevalent condition that is highly correlated with lifestyle factors such as diet and physical activity level (Centers for Disease Control and Prevention n.d., n.d.). The Australian Type 2 Diabetes Risk Assessment (AUSDRISK) (Baker Heart & Diabetes Institute, n.d.) is a scored survey that measures risk for type 2 diabetes by assessing ten risk factors: age, sex, ethnicity, smoking, diet, physical inactivity, family history of diabetes, history of high blood glucose, use of medication to treat high blood pressure, and waist circumference. These risk factors can be self-reported by an individual without the need to collect any anthropometric data, with the exception of waist circumference.

The AUSDRISK has proven to be a sufficient tool for assessing both risk of future type 2 diabetes incidence and identifying individuals with undiagnosed type 2 diabetes in many populations, across various countries, age groups, genders, and ethnic/racial groups (Chen et al., 2010; Kengne et al., 2014; Lotfaliany et al., 2019). Validation studies have found strong test-retest reliability and predictive value for type 2 diabetes incidence over a follow-up period of up to
10 years in individuals without type 2 diabetes at baseline (Abbasi et al., 2012; Chen et al., 2010).

Type 2 diabetes is a largely preventable disease. As it is strongly linked to lifestyle choices, such as those assessed in the AUSDRISK, onset can be avoided by proactively making healthy lifestyle choices, such as regular exercise and weight management (Mayo Clinic, 2019). Following onset, type 2 diabetes can be treated with a combination of lifestyle adjustments and blood glucose-lowering medications. For instance, Marín-Peña Alvarez et al. (2016) discuss the effectiveness of reducing dietary carbohydrate intake and increasing physical activity levels in addition to using hypoglycemia drugs to manage and lessen severity of type 2 diabetes.

The AUSDRISK is a validated instrument capable of identifying risk of future onset of type 2 diabetes as well as screening for undiagnosed type 2 diabetes. As effective interventions to reduce risk of onset and lessen severity of the disease are available, researchers that discover findings from AUSDRISK assessments that indicate elevated risk for type 2 diabetes should inform participants of these results.

**Example 3: Heavy drinking behavior questionnaire (AUDIT)**

Harmful alcohol consumption is the third leading preventable cause of death in the U.S. and is associated with many short-term and long-term health consequences, such as liver disease and several types of cancer (National Institute on Alcohol Abuse and Alcoholism, n.d.). The World Health Organization’s Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001) is a 10-question survey used to identify both risky drinking and diagnosable alcohol use disorders (AUD) with questions about alcohol consumption, dependence, and experience of alcohol-related harm. The AUDIT-C is an abbreviated version of the AUDIT, consisting of the original instrument’s three questions about alcohol consumption which may be used to identify risky drinking (National Institute on Drug Abuse, n.d.).

The AUDIT and AUDIT-C have been found to be effective tools for screening for risky drinking, DSM-IV and DSM-IV diagnosable alcohol use disorders, and other alcohol-related problems. These instruments have demonstrated usefulness across several age groups, racial/ethnic groups, and genders, indicating utility in a wide range of populations. Validation studies of the AUDIT have found strong internal consistency and test-retest reliability (Reinert and Allen, 2007). The AUDIT and AUDIT-C have demonstrated good discrimination for detection of both current AUD and risky drinking (Bush et al., 1998; Dawson et al., 2005; Frank et al., 2008), as well as high sensitivity and specificity for detection of risky drinking (Reinert and Allen, 2007). Additionally, higher AUDIT scores at baseline predict greater likelihood experiencing social, medical, and other alcohol-related problems in the future (Conigrave et al., 1995).
Risky drinking is a key determinant of elevated risk for DSM-diagnosable alcohol use disorder (Greenfield et al., 2014). Following responsible drinking guidelines may significantly reduce one’s likelihood of developing AUD in the future (Greenfield et al., 2014). Additionally, following onset, alcohol use disorder may be treated using behavioral therapies, medications, mutual support groups, and various other methods of treatment (National Institute on Alcohol Abuse and Alcoholism, 2010).

As the AUDIT and AUDIT-C are valid and reliable instruments for detection of risky drinking, current alcohol use disorder, and other alcohol-related problems, research participants should be made aware of any findings from these assessments that indicate risk for, or presence of, such conditions.

Discussion

The existing guidelines for returning incidental research findings to research participants set forth by most U.S. government and professional research organizations pertain only to biological test data, such as imaging results and genetic testing. Suggested criteria for returning findings to participants include determining the clinical significance and urgency of the findings, as well as asking for the participant’s consent to receive test results. The APA is the only major professional organization that we found to provide guidance for returning incidental findings arising from non-biological test data. The three examples of non-biological tests presented meet the criteria of (1) returning results that are based on a validated assessment process, (2) returning results that have implications for the future well-being of research participants, and (3) returning results which can be acted upon to limit, prevent, or decrease the risk of negative health consequences.

These are just three of many existing, validated, non-biological assessments that are capable of assessing risk or presence of preventable or treatable health conditions. Although we did not find published examples of incidental findings arising from the use of these tools in a research context, non-biological screening instruments can be used to screen for exclusionary health conditions in participants who are not suspected of having the specific condition, or disease for which these instrument identifies presence or risk. As suggested by Wolf (2013), incidental findings can arise during participant eligibility screening and baseline data collection. Despite compelling evidence that non-biological test data can have significant predictive value for health risks and outcomes, this form of data does not often feature in discussions and guidance for the reporting of incidental findings. Of course, we don’t know how often researchers actually return incidental findings arising from non-biological test data in practice. Maybe it does happen. Nevertheless, the scarcity of relevant academic discussion and limited policy motivated us to examine this issue. The lack of guidance leaves open the possibility that researchers are not informing participants of important health-related findings as standard. Development
or revision of guidance for incidental findings that includes non-biological test data could strengthen protections for human participants.

Accordingly, we recommend that research organizations and institutions, policy makers, researchers, and research ethics reviewers consider updating the scope of what is considered an incidental finding to include non-biological test data. Additional research to understand the experiences and opinions of stakeholders is needed to formulate these changes in a manner that is representative of real-world challenges and ethical duties. The three examples presented in this manuscript provide some evidence that non-biological test data can detect current disease or disease risk, which is potentially treatable or preventable, but the scope of non-biological test data that meets this threshold is poorly understood. Research focused on identifying commonly used assessments which reliably predict the onset of future disease could help researchers and research ethics policymakers strengthen protections for participants.

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Notes
1. Also commonly referred to as research ethics committees (RECs).
2. DSM = Diagnostic and Statistical Manual of Mental Disorders.

References
Abbasi A, Peelen LM, Corpeleijn E, et al. (2012) Prediction models for risk of developing type 2 diabetes: Systematic literature search and independent external validation study. BMJ 345: e5900.

APA (2011) Incidental findings in research with human participants: Ethical challenges for psychologists. Available at: https://www.apa.org/science/about/psa/2011/04/human-research (accessed 27 May 2021).

Babor TF, Higgins-Biddle JC, Saunders JB, et al. (2001) AUDIT: The Alcohol Use Disorders Identification Test, 2nd edn. Geneva: World Health Organization Department of Mental Health and Substance Dependence.

Baker Heart & Diabetes Institute (n.d.) Risk assessment tool for type 2 diabetes (AUSDRISK). Available at: https://baker.edu.au/health-hub/diabetes-risk-assessment (accessed 27 May 2021).

Bush K, Kivlahan DR, McDonell MB, et al. (1998) The AUDIT Alcohol Consumption Questions (AUDIT-C): An effective brief screening test for problem drinking. Archive of Internal Medicine 158: 1789–1795.
Centers for Disease Control and Prevention (n.d.) Type 2 diabetes. Available at: https://www.cdc.gov/diabetes/basics/type2.html (accessed 27 May 2021).

Centers for Disease Control and Prevention (n.d.) Diabetes risk factors. Available at: https://www.cdc.gov/diabetes/basics/risk-factors.html (accessed 27 May 2021).

Chen L, Magliano DJ, Balkau B, et al. (2010) AUSDRISK: An Australian type 2 diabetes risk assessment tool based on demographic, lifestyle, and simple anthropometric measures. The Medical Journal of Australia 192(4): 197–202.

Chlebowski C, Robins DL, Barton ML, et al. (2013) Large-scale use of the modified checklist for autism in low-risk toddlers. Pediatrics 131(4): e1121–e1127.

Conigrave KM, Saunders JB and Reznik RB (1995) Predictive capacity of the AUDIT questionnaire for alcohol-related harm. Addiction 90: 1479–1485.

Dawson DA, Grant BF, Stinson FS, et al. (2005) Effectiveness of the derived Alcohol Use Disorders Identification Test (AUDIT-C) in screening for alcohol use disorders and risk drinking in the US general population. Alcoholism Clinical and Experimental Research 29(5): 844–854.

Frank D, DeBenedetti AF, Volk RJ, et al. (2008) Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. Journal of General Internal Medicine 23(6): 781–787.

Greenfield TK, Ye Y, Bond J, et al. (2014) Risks of alcohol use disorders related to drinking patterns in the U.S. general population. Journal of Studies on Alcohol and Drugs 75(2): 319–327.

Kalia SS, Adelman K, Bale SJ, et al. (2017) Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics. Genetics in Medicine 19(2): 249–255.

Kengne AP, Beulens JW, Peelen LM, et al. (2014) Non-invasive risk scores for prediction of type 2 diabetes (EPIC-InterAct): A validation of existing models. The Lancet Diabetes & Endocrinology 2(1): 19–29.

Kleinman JM, Robins DL, Ventola PE, et al. (2008) The modified checklist for autism in toddlers: A follow-up study investigating the early detection of autism spectrum disorders. Journal of Autism and Developmental Disorders 38(5): 827–839.

Lotfaliany M, Hadaegh F, Asgari S, et al. (2019) Non-invasive risk prediction models in identifying undiagnosed type 2 diabetes or predicting future incident cases in the Iranian population. Archives of Iranian Medicine 22(3): 116–124.

McCallum JM, Arekere DM, Green BL, et al. (2006) Awareness and knowledge of the U.S. public health service syphilis study at Tuskegee: Implications for biomedical research. Journal of Health Care for the Poor and Underserved 17(4): 716–733.

Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, et al. (2016) Update on the treatment of type 2 diabetes mellitus. World Journal of Diabetes 7(17): 354–295.

Mayo Clinic (2018) Autism spectrum disorder. Available at: https://www.mayoclinic.org/diseases-conditions/autism-spectrum-disorder/diagnosis-treatment/drc-20352934 (accessed 27 May 2021).

Mayo Clinic (2019) Diabetes prevention: 5 tips for taking control. Available at: https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/in-depth/diabetes-prevention/art-20047639 (accessed 27 May 2021).

Munden RF, Carter BW, Chiles C, et al. (2018) Managing incidental findings on thoracic CT: Mediastinal and cardiovascular findings. A white paper of the ACR Incidental Findings Committee. Journal of the American College of Radiology 15(8): 1087–1096.
National Institute on Alcohol Abuse and Alcoholism (n.d.) Alcohol facts and statistics. Available at: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics (accessed 27 May 2021).

National Institute on Alcohol Abuse and Alcoholism (2010) Exploring treatment options for alcohol use disorders. Available at: https://pubs.niaaa.nih.gov/publications/aa81/aa81.htm (accessed 27 May 2021).

National Institute on Drug Abuse (n.d.) Instrument: AUDIT-C questionnaire. Available at: https://cde.drugabuse.gov/instrument/f229c68a-67ce-9a58-e040-bb89ad432be4 (accessed 27 May 2021).

National Institutes of Health (n.d.) Behavioral management therapy for autism. Available at: https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/behavioral-management (accessed 27 May 2021).

National Institutes of Health (n.d.) Early intervention for autism. Available at: https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/early-intervention (accessed 27 May 2021).

National Institutes of Health (n.d.) Social skills training for autism. Available at: https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/social-skills (accessed 27 May 2021).

National Institutes of Health (n.d.) Nutritional therapy for autism. Available at: https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/nutritional-therapy (accessed 27 May 2021).

National Institutes of Health (n.d.) Medication treatment for autism. US Department of Health and Human Services. Available at: https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/medication-treatment (accessed 27 May 2021).

Pandey J, Verbalis A, Robins DL, et al. (2008) Screening for autism in older and younger toddlers with the modified checklist for autism in toddlers. *Autism* 12(5): 513–535.

Presidential Commission for the Study of Bioethical Issues (2016) For IRB members: Incidental and secondary findings. Available at: https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/IRB%20Primer%20Incidental%20Findings%2010.30.16.pdf (accessed 27 May 2021).

Reinert DF and Allen JP (2007) The alcohol use disorders identification test: An update of research findings. *Alcoholism Clinical and Experimental Research* 31(2): 185–199.

Robins D, Fein D and Barton M (2009) Modified checklist for autism in toddlers. Revised with Follow-Up (M-CHAT-R/F).

Robins DL, Casagrande K, Barton M, et al. (2014) Validation of the modified checklist for Autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics* 133(1): 37–45.

Robins DL, Fein D, Barton ML, et al. (2001) The modified checklist for autism in toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. *Journal of Autism and Developmental Disorders* 31(2): 131–144.

Rothman DJ (1982) Were Tuskegee & Willowbrook ‘studies in nature’? *Hastings Center Report* 12(2): 5–7.

U.S. Department of Health & Human Services (2017) Recommendations on reporting incidental findings. Available at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-f-august-2-2017/index.html (accessed 27 May 2021).

Wolf SM (2013) Return of individual research results and incidental findings: Facing the challenges of translational science. *Annual Review of Genomics and Human Genetics* 14: 557–577.