Importance of the problem

- “Whether to divulge results…, and how, is arguably the most pressing issue in genetics today.”

- “one of the thorniest current challenges in clinical research”
  --Francis Collins, *NYT* 8/25/12

- NIH has created a Return of Results (RoR) Consortium to link funded investigators and support progress

- The Presidential Commission is doing a whole report now on these issues

- Dealing with return of results & incidental findings is a major challenge in both research & clinical genomics

- At stake is the future of autonomy & consent in genomics
Punchlines

- Research routinely generates IFs/IRRs of potential clinical or reproductive importance
- Dealing with this challenges the clinical/research dichotomy that has structured bioethics & health law
- Emerging consensus suggests that researchers have duties to return some IFs/IRRs
- Translation of genomics into clinical care makes the problem of incidental findings inescapable
- Recommendations for clinical genomics are emerging but highly controversial
Our work on these problems:

- Collaboration with Illes et al. (2006) on Trans-NIH/Stanford workshop on IFs in **neuroimaging**

- “Managing Incidental Findings in Human Subjects Research” NIH/NHGRI grant #1-R01-HG003178 (Wolf, PI)

- “Managing Incidental Findings and Research Results in Genomic Biobanks & Archives” NIH/NHGRI grant #2-R01-HG003178 (Wolf, PI)

- Collaboration on NHLBI workshop on IFs & IRRs in **genetics**, resulting in Fabsitz et al. (2010)

- “Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment” NIH/NCI/NHGRI grant #R01-CA154517 (Petersen, Koenig, Wolf, PIs); Brocher Centre Workshop in Switzerland, Nov. 2013 (w/Kaye, Elger)

- Robert Wood Johnson Foundation Investigator Award (Wolf, PI)
Definitions

- **Incidental Finding (IF)**: “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”

- **Individual Research Result (IRR)**: a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research on the focal variables under study in meeting the study’s aims

- **Aggregate Research Results**: findings concerning the research population (usually published) that are discovered in the course of research on the focal variables under study in meeting the study’s aims

--Wolf et al., *Journal of Law, Medicine & Ethics* 2008;36(2):219-48
Chief ethical principle governing WGS is respect for persons; that requires “fully informed consent,” stating “what data and information, if any, might be returned.” (3.2)

“Researchers, clinicians…must make individuals aware that incidental findings are likely to be discovered….”

The consent process should convey whether these findings will be communicated, the scope of communicated findings, and to whom the findings will be communicated.” (3.3)

No position taken on scope or process for returning IFs/IRRs, though a project focusing on IFs is now under way.
Key questions re handling IFs & IRRs in research

- What criteria define returnable IFs/IRRs? Do these include IFs/IRRs of reproductive significance? Personal significance?
- Do researchers have a duty to look for IFs/IRRs in their data?
- What should researchers do once they spot a suspected IF/IRR? Evaluate how? Seek a consult?
- Does return require confirmation in a CLIA-certified lab?
- What should be disclosed to the research participant or participant’s physician and how?
- What should research protocols & consent forms say in advance about managing IFs/IRRs?
- What should IRBs & funders require?
IFs & IRRs bridge research & clinical care

- IFs & IRRs are discovered in the course of research, but have clinical, reproductive, and personal implications.

- IFs include findings that are well understood, with established analytic validity and clinical utility—findings routinely communicated in clinical care.

- IRRs are findings generated in pursuit of research aims, but recommendations urge returning the subset with analytic validity, clinical utility, and high health significance.

- Attitudinal research suggests many participants want return.

- The problem of IFs & IRRs thus challenges the foundational dichotomy between research & clinical care (Wolf 2010).
Doctor-patient
- MD owes duty of clinical care
- Duty is to serve pt.’s interests
- Patient can sue for damages
- Retrospective adjudication of fault & liability
- Governed by state tort and contract law
- Guided by ethics codes
- **Info disclosed**: professional standard of care & info material to patient choice, values

Researcher-participant
- Researcher owes little clinical care
- Duty is to seek generalized knowledge
- Participant generally can’t sue under research regs; use tort law
- Prospective screening of proposed protocols by IRBs
- Governed by federal regs. on human research (Common Rule, FDA regs.)
- No ethics codes until Nuremberg
- **Info returned**: ??
Project recommendations on IFs/IRRs:
(Wolf et al. 2008, 2012)

- Researchers do shoulder **duties to manage IFs/IRRs**
- Researchers should **address management of IFs in protocol & in consent process; get IRB approval**

**Should return** IFs/IRRs that:
- **are analytically valid & in compliance with law** (e.g., CLIA)
- **reveal established & substantial risk of a serious health condition**
- **are actionable** (significant potential to alter onset, course, or tx)
- **if return is consented to by participant** (at initial consent or after)

**May return** additional IFs/IRRs if:
- **they reveal established & substantial risk of likely health or reproductive importance, or personal utility**
- **return is likely to provide net benefit**
Other recommendations:

- **Fabsitz et al.** (2010) (under NHLBI auspices):
  - Researchers **should return** results if participant consents and:
    - finding has **important health implications** & risks are established, substantial
    - finding=**actionable** (potential to change disease course), and
    - test=**analytically valid**; disclosure **comports with law** (e.g., CLIA)
  - Researchers **may return** other results if participant consents and:
    - potential **benefits outweigh risks** from participant’s perspective (e.g., reproductive risks, personal meaning, health risks)
    - **IRB approves** disclosure plan, and
    - test=**analytically valid**; disclosure **comports with law** (e.g., CLIA)

A **central advisory body** should recommend the roster of returnable genetic findings.
BUT—all of that is in the context of research

- So key objections/concerns have been
  - Diversion of resources from research to return of IFs/IRRs for clinical purposes
  - Imposition of clinical duties on researchers who may not have the proper expertise
  - Potential confusion between research and clinical care in the minds of participants, encouraging the therapeutic misconception
  - In other words, that research should stay on the research side, separated from clinical care
Clinical integration of WGS is under way

- “[G]enomic sequencing approaches can be of great value in the clinical evaluation of individuals with suspected germ-line genetic disorders....[T]here are already instances in which genomic sequencing approaches can and should contribute to clinical care.” —ACMG Board of Directors, *GIM* (2012)

- Many anticipate a future of affordable sequencing that is readily available.
What standards should govern return in clinical WGS?

- Berg et al.—Deploying clinical WGS & using “bins” (2011):
  - Clinicians **should return** Bin 1 results:
    - “medically actionable”
    - “direct clinical utility based on the current medical literature”
    - “known to cause disease or strongly predicted to disrupt function”
  - Clinicians **may return** Bin 2 results:
    - “clinically valid but not directly actionable”
    - some patients may wish this information
    - Bin 2A—low risk, doubtful current utility
    - Bin 2B—medium risk but incomplete penetrance, doubtful utility, may cause **distress** (includes carrier state of reproductive signif.)
    - Bin 2C—may cause high distress
  - Clinicians **should not return** Bin 3 results:
    - variants of no or unknown clinical significance
ACMG 2012 approach in clinical WGS/WES:

ACMG Policy Statement (2012):

- IFs “are highly likely, if not inevitable” in WGS/WES
- Labs & clinics need policies on disclosure of IFs; share policy with patients
- Before testing, counsel individuals on what “will or will not be disclosed”
- Allow patients to opt-out of receiving some IFs, tho’ “exceptional” cases may arise
- When screening asymptomatic individuals, set standards for return high to avoid reporting multiple false-positives (vs. diagnostic testing in affected patients)
ACMG’s 2013 approach in clinical WGS/WES:

ACMG (Green et al. 2013) -- “Recommendations for Reporting of Incidental Findings in Clinical…Sequencing”

- Specifies “minimum list” of 57 additional genes that labs should analyze when they perform sequencing for another indication (=genes associated with specific cancers, cardiovascular conditions, Malignant hyperthermia)
  - No consent sought from patient to analyze these specific genes
  - Patient who does not want IFs must decline sequencing altogether
- Labs should ascertain the gene variants of:
  - known or expected pathogenicity, high penetrance, actionability
- Lab must report these to clinician
- Clinician must report these to patient
  - No consent sought from patient to return this information
  - No “right not to know”
- Failure to report is “unethical” (ACMG “clarification” 2013)
Debate in *Science* (published May 31)

**Patient Autonomy and Incidental Findings in Clinical Genomics**

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Returning genetic incidental findings without patient consent is misguided.

**Ethics and Genomic Incidental Findings**

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Laboratories have an obligation to report clinically beneficial incidental findings.
ACMG 2013--debate:

Ensuing controversy:

- ACMG Working Group “did not favor offering the patient a preference as to whether or not to receive the minimum list of incidental findings….

  We recognize that this may be seen to violate existing ethical norms regarding the patient’s autonomy and ‘right not to know’ genetic risk information.”

- Appears to contradict prior ACMG policy that “Patients should be given the option of not receiving…secondary findings.” (2012)

On children--

- ACMG urges ascertainment & reporting regardless of patient’s age
- However, long-standing consensus (and ASHG/ACMG/AAP policy) is to restrict genetic testing in children to that medically necessary before the child reaches adulthood and can decide for him-/herself
- AAP/ACMG recently reiterated this standard—child’s own best interests
- New ACMG recommendations on IFs contradict that consensus
- Following consensus, child could be offered findings at majority
Where do we go next in clinical WGS/WES?

- We have guidelines on returning IFs/IRRs in research
- They generally require participant consent to receive IFs, but limit the further role of participant preferences in:
  - defining “actionability” (reproductive? personal utility?)
  - determining what will be returned in a given project (should/may)
  - permitting participants to choose to receive more info than “should”
- Clinical integration of WGS/WES requires considering greater physician duties to offer information to patients (in contrast to researcher duties to participants)
- It supports a more patient-centered approach
- Patient autonomy & decisional rights should apply to genomics too
Conclusion

- Problem of return of results & IFs is translational, about moving info from the research side across to the clinical side, due to its clinical significance—a bridge problem.

- Research guidelines for return generally offer limited info, with a limited role for participant preferences; these recommendations are under challenge from both sides (maintain researcher control & give less info vs. allow more participant control & give more info).

- Clinical integration of WGS/WES switches to the clinical sphere, doctor/pt relationship, clinical norms of disclosure: more disclosure & deference to patient values.

- Clinical genomics should embrace clinical norms of respect for patient choice & the necessity of patient consent.
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