Ethical Challenges of Genome-based Cancer Research

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Next-Generation Sequencing
A New Era!

"The era of the $1000 genome"

The cost of sequencing a single genome has dropped from 10M to <10K.

This has led to accelerations in genomic research and clinical medicine

www.genome.gov; Sheridan C. Nature Biotechnology , 2014. 32:115

Personalized Medicine

- The ability to tailor prevention, treatment or screening of individual patients based on their genotype, and to translate those recommendations into modified patient behaviors and improved outcomes

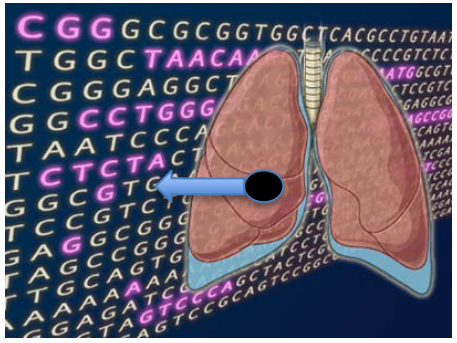
- Evidence-based examples in oncology
  - Germline: *BRCA1/2*
  - Somatic: HER2-neu, EGFR, *BRAF*

Burke, W. and B.M. Psaty, Jama, 2007. 298(14): p. 1682-4. Schwartz, G.F., et al., Cancer, 2008. 113(10): p. 2627-37. Robson, M.E., et al., J Clin Oncol. 28(5): p. 893-901. Chabner, BA et al. The Oncologist, 2013. 18:640. Chapman PB et al. NEJM 364:2507, 2011

Emerging Applications in Cancer Care

- Multiplex panels for cancer susceptibility
  - To identify individuals at high risk for cancer to tailor and maximize benefits, minimize harms with cancer screening and prevention

- Genomic Tumor Profiling
  - To identify molecular “drivers” of individual cancers and identify drugs targeting these pathways



Domchek S et al. , JCO 31: 1267, 2013; Mauer CB et al. Gen Med, Oct 10 2013 ; Garraway LA. J Clin Onc 31:1806, 2013

From single gene to multi-gene and whole genome applications

- Benefits
  - Gene discovery and coverage
  - Time, tissue and cost efficiencies

- Challenges
  - Various platforms
  - Interpretation
  - Uncertainty
  - Secondary information

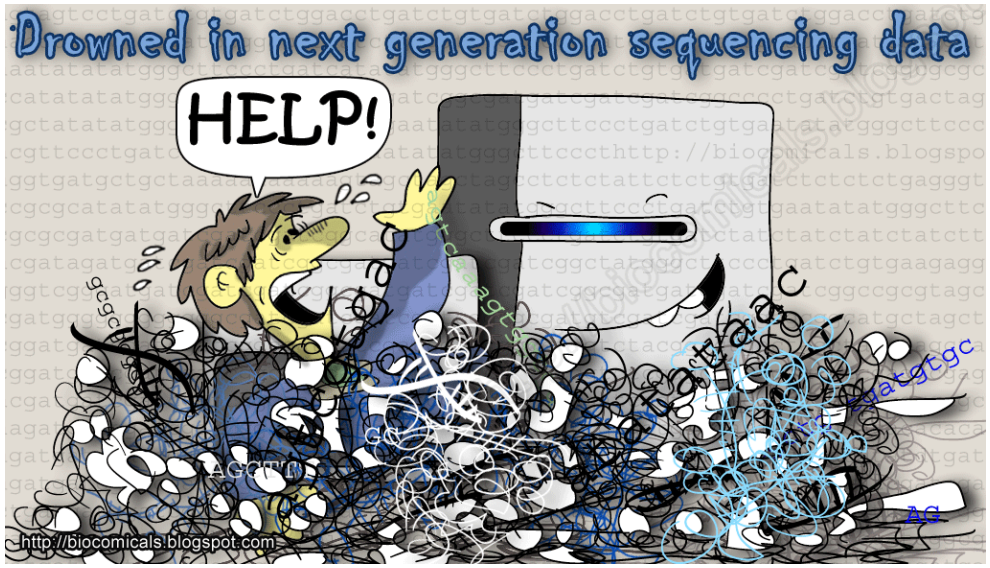
Berg JS et al. Gen Med 13:6, 2011; Presidential Commission for the Study of Bioethical Issues, Anticipate and Communicate. Dec 2013

ELSI & Genomics

- Risks, benefits & utilities
- Informed consent
- Obligations to return individual research results
- Obligations to return incidental findings
- Privacy and data sharing
- Justice, cost and access

The post-genome era in the clinics: Are we ready?

"Physicians are still a long way from submitting their patients full genomes for sequencing, not because the price is high, but because the data are difficult to interpret" *Varmus, NEJM 2010*



Session 3: Ethical Challenges of Genome-based Cancer Research

- Return of individual research results
  - Angela R. Bradbury, MD
- ROR & Incidental findings
  - Gail Jarvik, MD, PhD
- Liability and other challenges
  - Ellen Wright Clayton, MD, JD
- Use of archived biospecimens
  - Jeffrey Peppercorn, MD, MPH

Return of Individual Research Results in Genomic Cancer Research

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Genomic studies and IRR

- As large prospective cohort studies with banked DNA have become increasingly utilized to evaluate the effects of genes, the environment and lifestyle, there has been increasing debate over the obligations, if any, to share individual research results with research participants.

Kaufman, D., et al., Genet Med, 2008. 10(11): p. 831-9.

NO: The case for not returning IRR

- Blurring of the distinction between research and clinical care
- The potential for misunderstanding or over-interpretation of clinical significance
- Maintaining privacy and the right not to know

National Bioethics Advisory Commission, 1999; Clayton, E.W. and A.L. McGuire, Genet Med, 2012. 14(4): p. 473-7; Beskow, L.M., Am J Bioeth, 2006. 6(6): p. 38-40; author reply W10-2; Meltzer, L.A, Am J Bioeth, 2006. 6(6): p. 28-30; author reply W10-2; Clayton, E.W. and L.F. Ross, JAMA, 2006. 295(1): p. 37; author reply 37-8; Knoppers, B.M., et al., Eur J Hum Genet, 2006. 14(11): p. 1170-8.

NO: The case for not returning IRR

- Prohibitive costs for research team, biobanks, health care system

- The potential negative impact on research progress

Dressler, L.G. and E.T. Juengst, Am J Bioeth, 2006. 6(6): p. 18-20; author reply W10-2. Bledsoe, M.J., et al., Genet Med, 2013. 15(2): p. 103-5. Bledsoe, M.J., et al., Genet Med, 2012. 14(4): p. 478-83. Klitzman, R.. Am J Bioeth, 2006. 6(6): p. 34-6; author reply W10-2.

YES: The case for returning IRR

- Beneficence
- Autonomy & respect for persons
- Reciprocity

- The duality of research and clinical care in cancer research

Manolio, T.A., Am J Bioeth, 2006. 6(6): p. 32-4; author reply W10-2.; Fernandez, C.V. and C. Weijer, Am J Bioeth, 2006. 6(6): p. 44-6; author reply W10-2. Fernandez, C.V., et al., Pediatr Blood Cancer, 2007. 48(4): p. 441-6. Ravitsky, V. and B.S. Wilfond, Am J Bioeth, 2006. 6(6): p. 8-17. Fryer-Edwards, K. and S.M. Fullerton, Am J Bioeth, 2006. 6(6): p. 36-8; author reply W10-2. Sharp, R.R. and M.W. Foster, Am J Bioeth, 2006. 6(6): p. 42-4; author reply W10-2. Beskow, L.M. and W. Burke,. Sci Transl Med, 2010. 2(38): p. 38cm20. Richardson, H.S. and L. Belsky, Hastings Cent Rep, 2004. 34(1): p. 25-33. Kollek, R and Petersen, I. J Med Ethics, 2011. 37:271. Bredenoord AL, et al. Hum Mut, 2011. 32(8):861.

SOMETIMES

- Select results (e.g. those that are clearly clinically actionable and have been confirmed in a CLIA lab) should be returned

- Informed consent should address return of individual research results

Clayton, E.W. and A.L. McGuire, Genet Med, 2012. 14(4): p. 473-7. Wolf SM et al. Genet Med, 2012. 14(4):p.361. Bookman, E.B., et al., Am J Med Genet A, 2006. 140(10): p. 1033-40. Greely, H.T., Annu Rev Genomics Hum Genet, 2007. 8: p. 343-64.?FABSITZ,

Case example (1)

- Participants in a large cancer registry recruited > 10 years ago, informed consent clearly stated no return of results. *BRCA1/2* mutations have been identified in research labs.

  – *Should IRR be returned?*
  – *Does current engagement matter?*
  – *Who pays for return and confirmation testing?*

Case example (2)

- Pancreatic cancer patients enrolled in research, informed consent includes return of "clinically significant results". *BRCA1/2* mutations have been identified in research labs. Many participants are now deceased.

  – *Should IRR be returned to next of kin?*
  – *Who pays for return and confirmation testing?*

Case example (3)

- *BRCA1/2* negative women enroll in study to identify other “cancer genes”. Informed consent includes return of “clinically significant results”. Multiplex research testing has identified high and moderate penetrance genes, which are now clinically available but of variable clinical utility.

  - *Should results be returned? Which ones?*
  - *Who pays for return and confirmation testing?*
  - *Does context matter?*

1. Defining “actionability” and “utility”

- The clinical utility or “actionability” of results is a deciding factor for many, although defining “actionability” is challenging
  - Commercially available?

- Broader conceptualizations of utility (e.g. personal, economic, future utility) have been proposed

Fullerton, SM et al. Genet Med, 2012. 14:4; Wolf SM et al. Genet Med, 2012. 14(4):p.361. Ravitsky, V. and B.S. Wilfond,. Am J Bioeth, 2006. 6(6): p. 8-17. Roberts, J.S., et al., J Empir Res Hum Res Ethics, 2010. 5(3): p. 17-30. Khoury, M.J., et al., Genet Med, 2009. 11(8): p. 559-67. Bollinger, J.M., et al., Genet Med, 2012. 14(4): p. 451-7. Grosse, S.D. and M.J. Khoury, Genet Med, 2006. 8(7): p. 448-50.; Foster, M.W., J.J. Mulvihill, and R.R. Sharp, Genet Med, 2009. 11(8): p. 570-4

2. Many research participants are interested in receiving IRR

- In a large public opinion survey, 90% of people expressed interest in receiving IRR, even if there was "nothing they could do"

- Focus groups have revealed similar interest in access to IRR, even if results are not immediately useful or there is uncertainty

Kaufman, D., et al., Genet Med, 2008. 10(11): p. 831-9; Fernandez, C.V., et al., Pediatr Blood Cancer, 2007. 48(4): p. 441-6; *Sharp, R.R. and M.W. Foster,* Am J Bioeth, 2006. 6(6): p. 42-4; author reply W10-2; Arar, N., et al., Public Health Genomics, 2010. 13(7-8): p. 431-9; Meulenkamp, T.M., et al., Am J Med Genet A, 2010. 152A(10): p. 2482-92; Beskow, L.M. and S.J. Smolek, J Empir Res Hum Res Ethics, 2009. 4(3): p. 99-111; O'Daniel, J. and S.B. Haga, Public Health Genomics, 2011. 14(6): p. 346-55; Biesecker, L.G., Genet Med, 2012. 14(4): p. 393-8; Murphy, J., et al. Am J Bioeth, 2008. 8(11): p. 36-43. Bollinger, J.M., et al., Genet Med, 2012. 14(4): p. 451-7.

3. What are the outcomes of returning IRR (risks, benefits and utilities)?

- 50-70% of those who spoke with a genetic counselor elected to receive results
  - Most did not cover confirmatory CLIA testing

- Satisfaction and well-being were high, cancer screening behaviors increased post-disclosure, regardless of test result

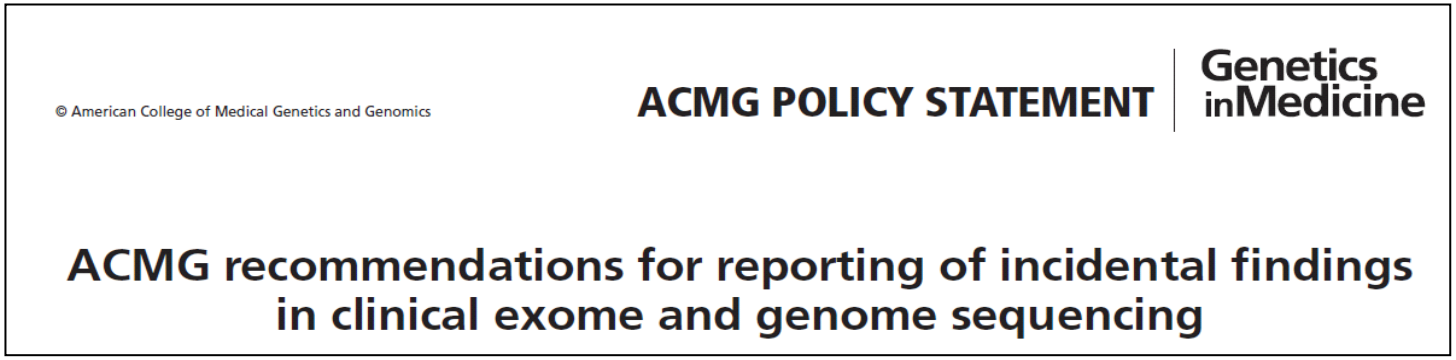
- Other ongoing studies (eMERGE, ClinSeq, CSER)

Graves, K.D., et al., Genet Med, 2013; Christensen, K.D., et al., Cancer Epidemiol Biomarkers Prev, 2011. 20(3): p. 522-9.; Siegfried, J.D., et al J Genet Couns, 2013. 22(2): p. 164-74; Glanz, K., et al., Cancer Epidemiol Biomarkers Prev, 2013. 22(4): p. 607-14.

4. Cost: What are they and who covers them?

- The associated costs of returning IRR are unknown
  - Re-contact, genetic counseling, confirmation testing and medical recommendations
- Who should bear the costs has not been resolved
  - Research team, biobank, health care system

Wolf, S.M., Annu Rev Genomics Hum Genet, 2013. 14: p. 557-77.; Dressler, L.G. and E.T. Juengst,. Am J Bioeth, 2006. 6(6): p. 18-20; author reply W10-2; Bledsoe, M.J., et al., Genet Med, 2012. 14(4): p. 478-83; Bledsoe, M.J., et al., Genet Med, 2013. 15(2): p. 159-60; Clayton, E.W., Cancer Epidemiol Biomarkers Prev, 2012. 21(2): p. 260-1.



- Developed a “minimum list” of 56 genes (23 cancer susceptibility genes) which should be reported as “incidental findings”
  - Regardless of indication for testing
  - Regardless of age
  - Regardless of patient preference
  - Includes the normal sample of a tumor-normal sequenced dyad

Green et al. GIM 15:565, 2013

Presidential Commission Recommendations for Return of IRR

- Anticipate and communicate
  - Informed consent outline plans and methods to opt-out if permitted
- Development of guidelines and best practices
- Fund research to evaluate benefits, harms
- Education for all stakeholders
- Ensure access and a supportive health system

Presidential Commission for the Study of Bioethical Issues, Anticipate & Communicate. Dec 2013

Research and guidance are needed

- **When is there an obligation to return IRR?**
- **Is it permissible to return IRR?**
  - *Which results, how?*
  - *Is confirmation in a CLIA lab necessary prior to return?*
  - *Who covers costs?*
  - *How does context impact these obligations?*
  - *What is the duration of obligations?*