BRIEF REPORT

Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

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IOM's Genomics Roundtable Workshop: Integrating Large-Scale Genomic Information into Practice

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ORIGINAL ARTICLE

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

Exome sequencing identifies the cause of a mendelian disorder

Sarah B Ng[1,10], Kati J Buckingham[2,10], Choli Lee[1], Abigail W Bigham[2], Holly K Tabor[2,3], Karin M Dent[4], Chad D Huff[5], Paul T Shannon[6], Ethylin Wang Jabs[7,8], Deborah A Nickerson[1], Jay Shendure[1] & Michael J Bamshad[1,2,9]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NT5E Mutations and Arterial Calcifications

Cynthia St. Hilaire, Ph.D., Shira G. Ziegler, B.A., Thomas C. Markello, M.D., Ph.D., Alfredo Brusco, Ph.D., Catherine Groden, M.S., Fred Gill, M.D., Hannah Carlson-Donohoe, B.A., Robert J. Lederman, M.D., Marcus Y. Chen, M.D., Dan Yang, M.D., Ph.D., Michael P. Siegenthaler, M.D., Carlo Arduino, M.D., Cecilia Mancini, M.Sc., Bernard Freudenthal, M.D., Horia C. Stanescu, M.D., Anselm A. Zdebik, M.D., Ph.D., R. Krishna Chaganti, M.D., Robert L. Nussbaum, M.D., Robert Kleta, M.D., Ph.D., William A. Gahl, M.D., Ph.D., and Manfred Boehm, M.D.

REPORT

HUMAN GENETICS

Whole-Genome Sequencing for Optimized Patient Management

Matthew N. Bainbridge,[1,2] Wojciech Wiszniewski,[3] David R. Murdock,[1] Jennifer Friedman,[4,5] Claudia Gonzaga-Jauregui,[3] Irene Newsham,[1] Jeffrey G. Reid,[1] John K. Fink,[6,7] Margaret B. Morgan,[1] Marie-Claude Gingras,[1] Donna M. Muzny,[1] Linh D. Hoang,[8] Shahed Yousaf,[8] James R. Lupski,[1,3,9,10] Richard A. Gibbs[1,3]*

Bioinformatics will soon be the rate limiting step

- How do we extract information from WGS?
- What information should be extracted? Information will be available and won't be interpretable right now, but will be interpretable in the future: what is the duty to reinterpret and re-contact the patients? New implications will be constant with continued revision.
- Who will decide what gets filtered down and when? (Lab, PCP, genetics specialist, the patient?)
- Is it ever appropriate to suppress information?
- Do you only look at the part of the result that tells you one thing?
- Can you leave the raw data just sitting there? Where is it to be stored?
- Can you only do partial analysis of the data?
- Will patients own the process? If they have their own genome, will they have control over when and what gets analyzed?
- How do you integrate results given directly to the patients back into the medical record?
- How long will data generated and stored at DTC companies be available?
- Will a genome be sequenced again over time?

How do you add and interpret additional layers?

- Genome alone
- Epigenetics

Workforce issues

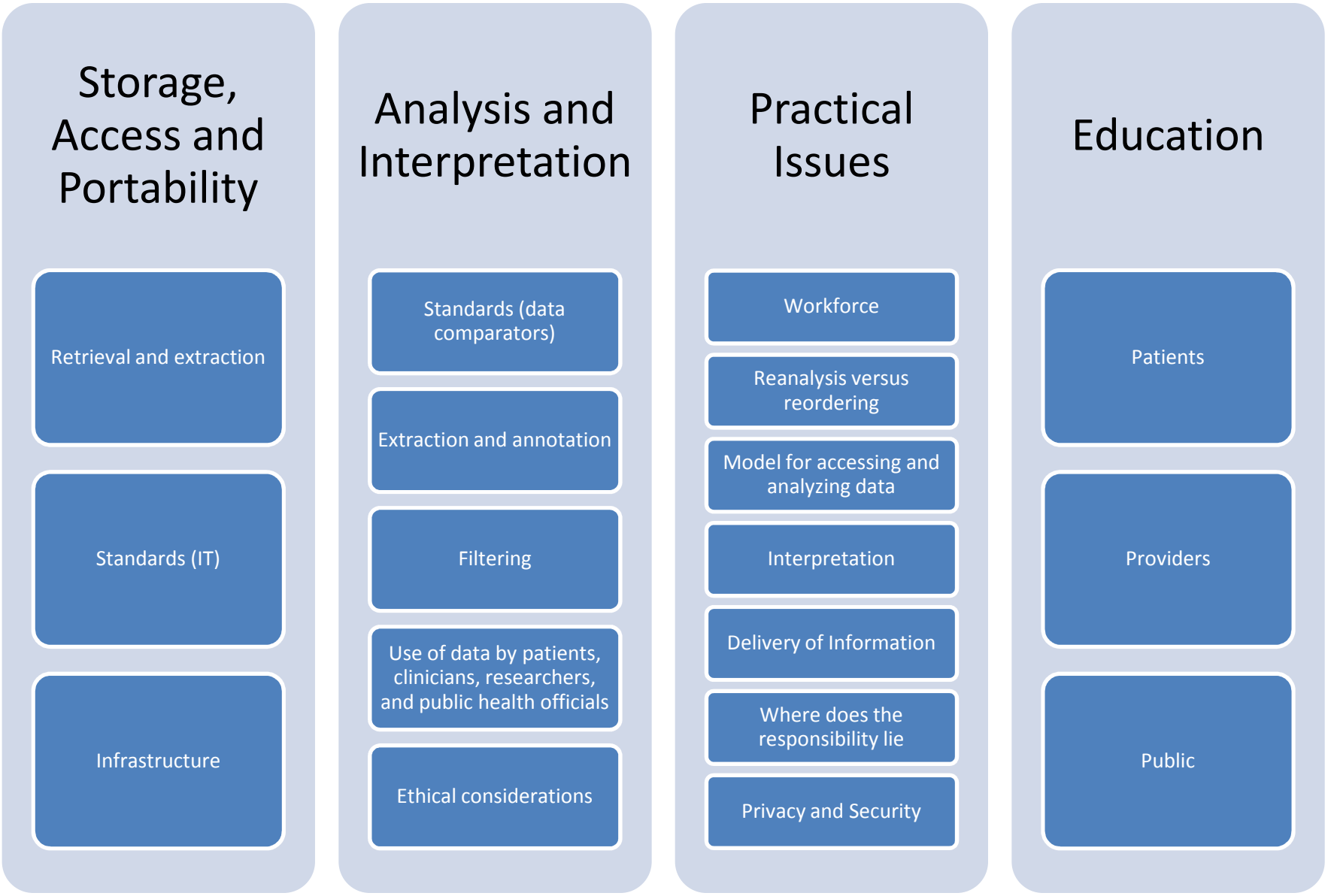
- Individuals who can help manage and transfer this data/filter etc.
- How do we ensure adequate communication ability between the bioinformatics workforce and clinicians?
- How do we prepare newly training and existing bioinformaticists to understand the genetics piece?
- Likewise, how do we prepare the genetics workforce to understand the bioinformatics piece?

Issues with informed consent

- How do you get appropriate consents at the beginning?
- Some companies put the onus on the patients.
- Nuances of consent and re-contact.
- Will the issue of having someone else know this information change how people decide if they want it?

Stewardship/Ownership

- Who will be the "keeper" of this information?
- Who owns the data?
- What happens when someone dies?
- What about questions of paternity?
- How do we filter the information so the useful parts are kept and accessible?


Storage, Access and Portability
Retrieval and extraction
Standards (IT)
Infrastructure
Analysis and Interpretation
Standards (data comparators)
Extraction and annotation
Filtering
Use of data by patients, clinicians, researchers, and public health officials
Ethical considerations
Practical Issues
Workforce
Reanalysis versus reordering
Model for accessing and analyzing data
Interpretation
Delivery of Information
Where does the responsibility lie
Privacy and Security
Education
Patients
Providers
Public

Workshop Assumptions and Caveats

Sequencing technology will advance enough to produce clinically meaningful results	Large-scale genomic analyses will be cost-effective and comparable to other diagnostic tests	Whether genomic technologies should be utilized in practice is not at debate.