Legal, Regulatory, and Ethical Issues in the Secondary Use of Genomic Data

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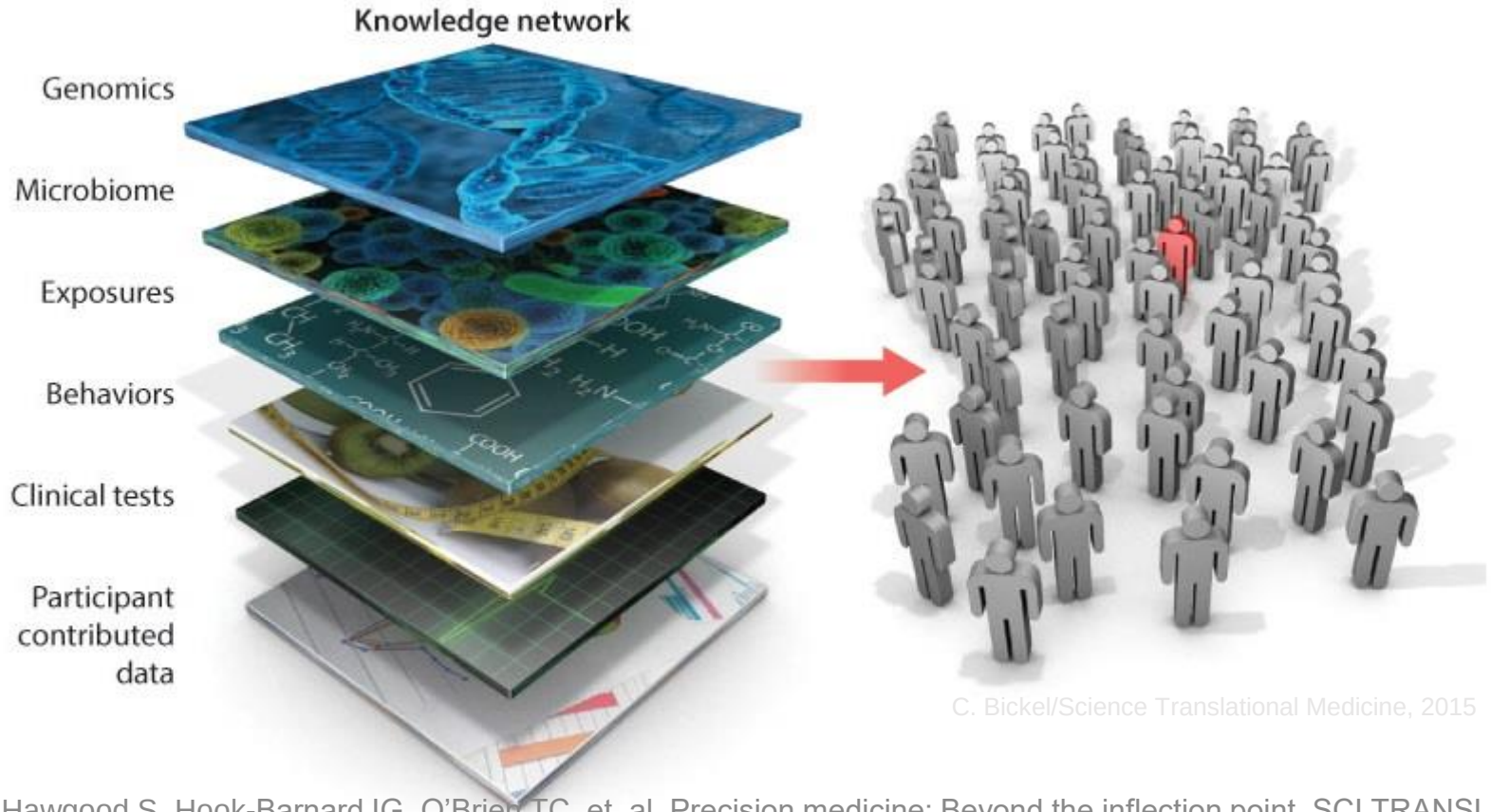
Outline

- There are a lot of clinical data available.
- Genomic data are and will be available on many patients through biobanks, research studies, clinical trials, and clinical genomic tests.
- Consents for data use span over a long period of time, often before we envisioned what we would do with the data. How can the data be used?
- What are the proposed changes to the Common Rule, and what will the impact be?

Precision medicine allows us to surpass a “single-layer” healthcare

We need to align and integrate diverse, often unstructured, data sets into a comprehensive knowledge network if we are to understand the complexities of human health and disease.



Hawgood S, Hook-Barnard IG, O’Brien TC, et. al. Precision medicine: Beyond the inflection point. SCI TRANSL MED 2015; 7(300): 300.

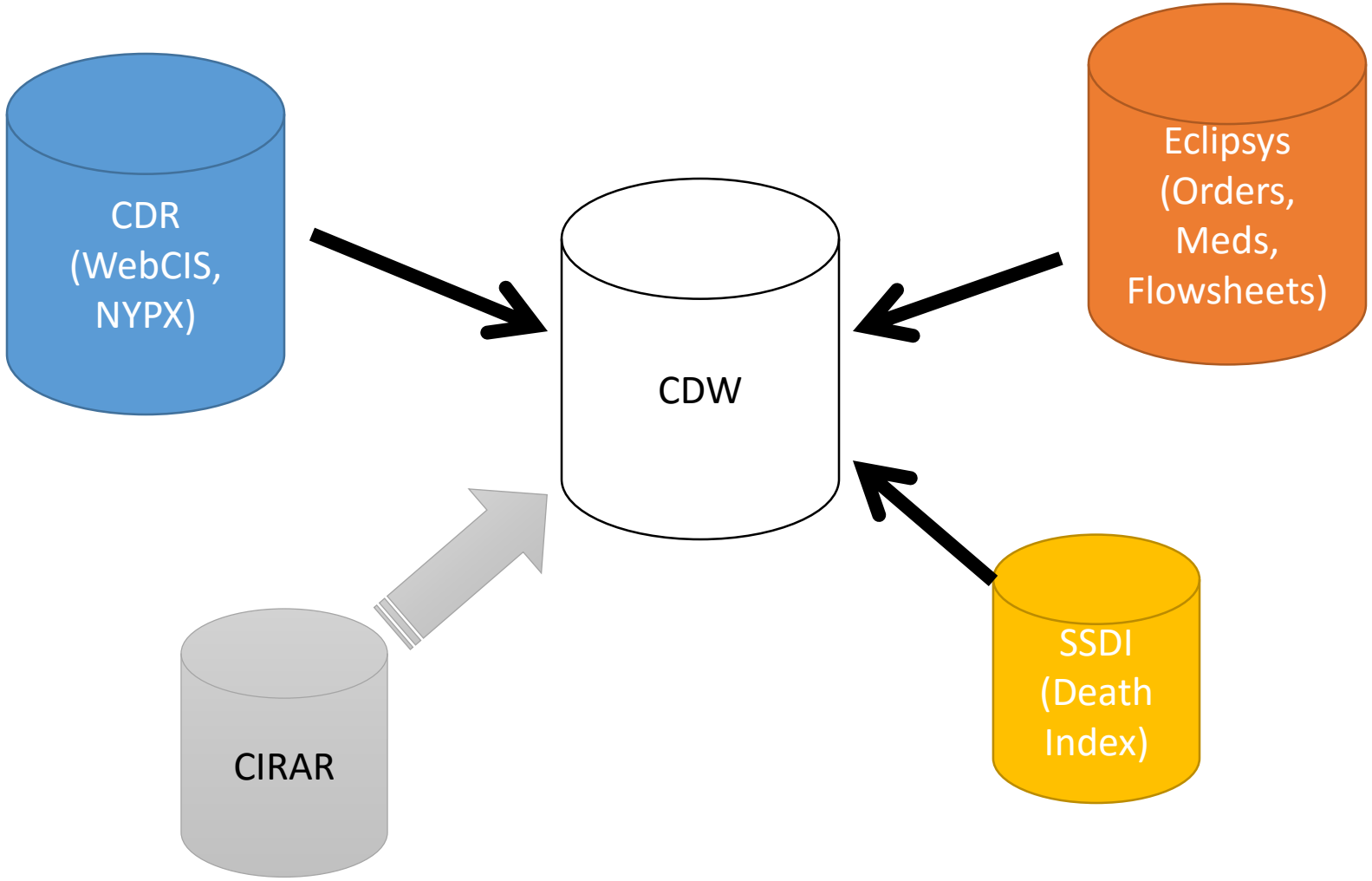
Why now? From the numbers perspective…

	10 years ago	2016
Cost of sequencing a human genome	$22,000,000	$1,500
Amount of Time to Sequence a Human Genome	2 years	<1 day
Number of smart phones in the United States	1 million (<2%)	160 million (58%)
EHR Adoption (% hospitals)	20-30%	>90%
Computing Power	n	nx16

Opportunities for EMRs in Medicine

- Standardization of data collection
- Engagement of the patient through their health portal, including education and decision support
- Engaging patients to partner in research and retaining research cohorts
  - May include returning individual research results to patients in addition to aggregate research results
- Data mining to improve the quality of care and perform research
- Storage of genomic data and iterative reinterpretation

Data in the Columbia Clinical Data Warehouse from 1994



What data are available?

- Patient demographics
- Visit history
- Diagnoses
- Procedures
- Vital signs
- Medications
- Flowsheet elements
- Structured notes
- Unstructured notes (mined by natural language processing)
- Genetic/genomic data

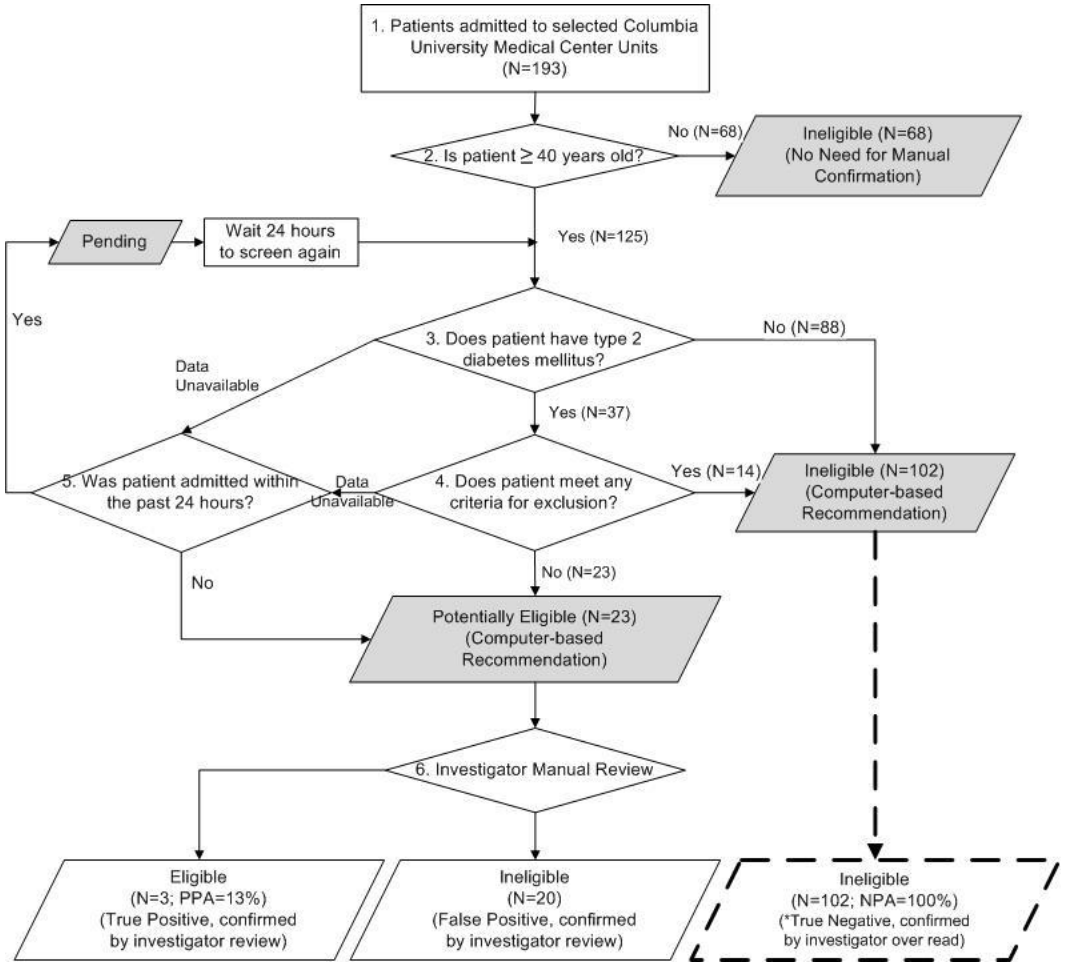
Other Data (2015)

Data type	Count
Diagnoses	3.3M
Procedures	570K
Lab tests	22M
Medications	1.5M
Vital signs	~80% of patients
Flowsheet/structured elements	400M
Notes	6.3M

De-identified Data Can Be Used to Address Clinical Questions

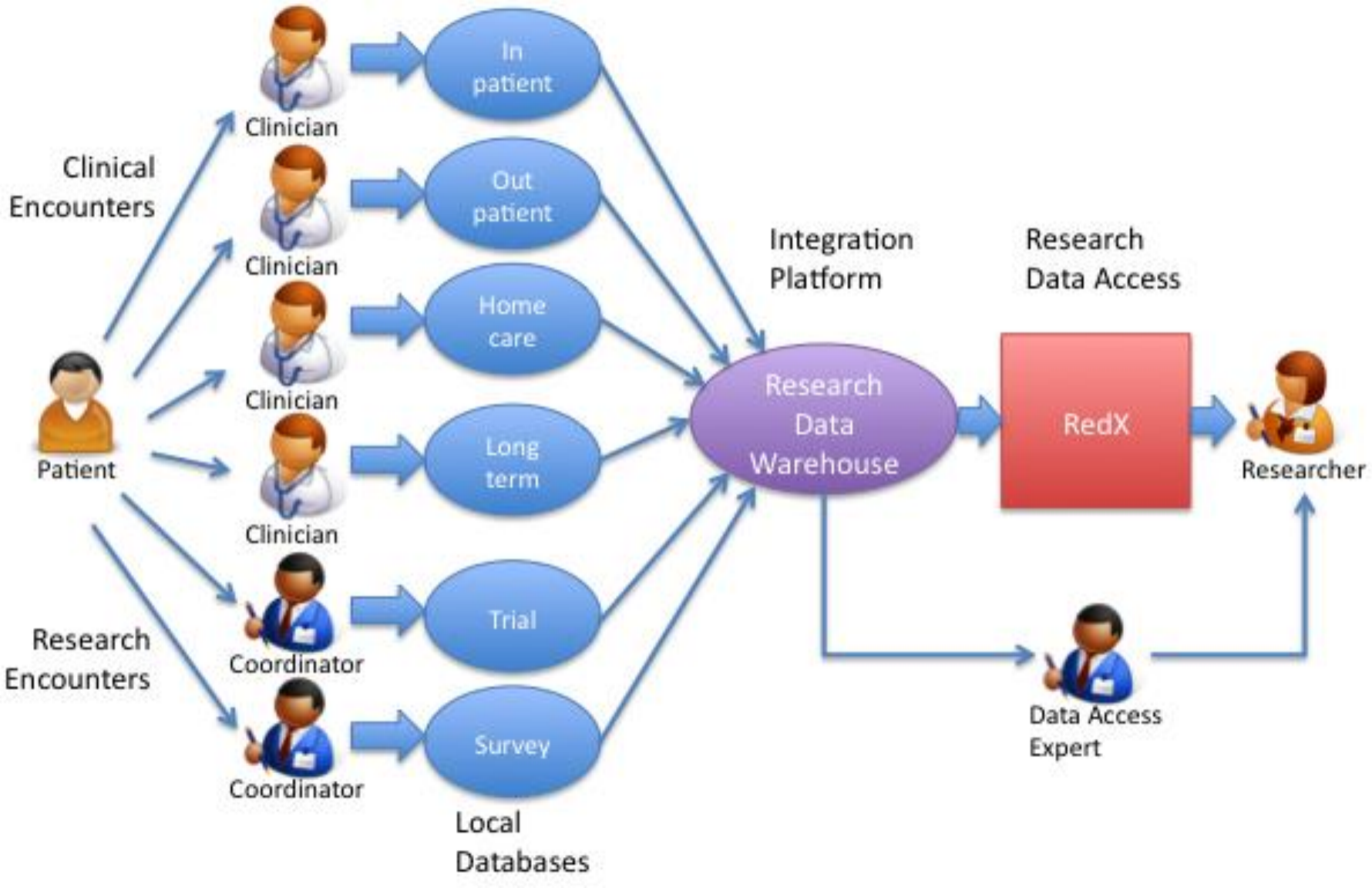
- Remove all patient identifiers
  - Name, address, MRN, etc.
  - Unlinked research identifier
  - Fake patient name
- No free text
- All dates shifted down 0-365 days
- All patients over 85 years → 85 years old
- Some data binning for continuous data

E-Screening for Study Eligibility



Thadani *J Am Med Inform Assoc,* 2009, 16(6), 869-873.

Combining Research and Clinical Care in WICER



Larger Aggregated Clinical Datasets

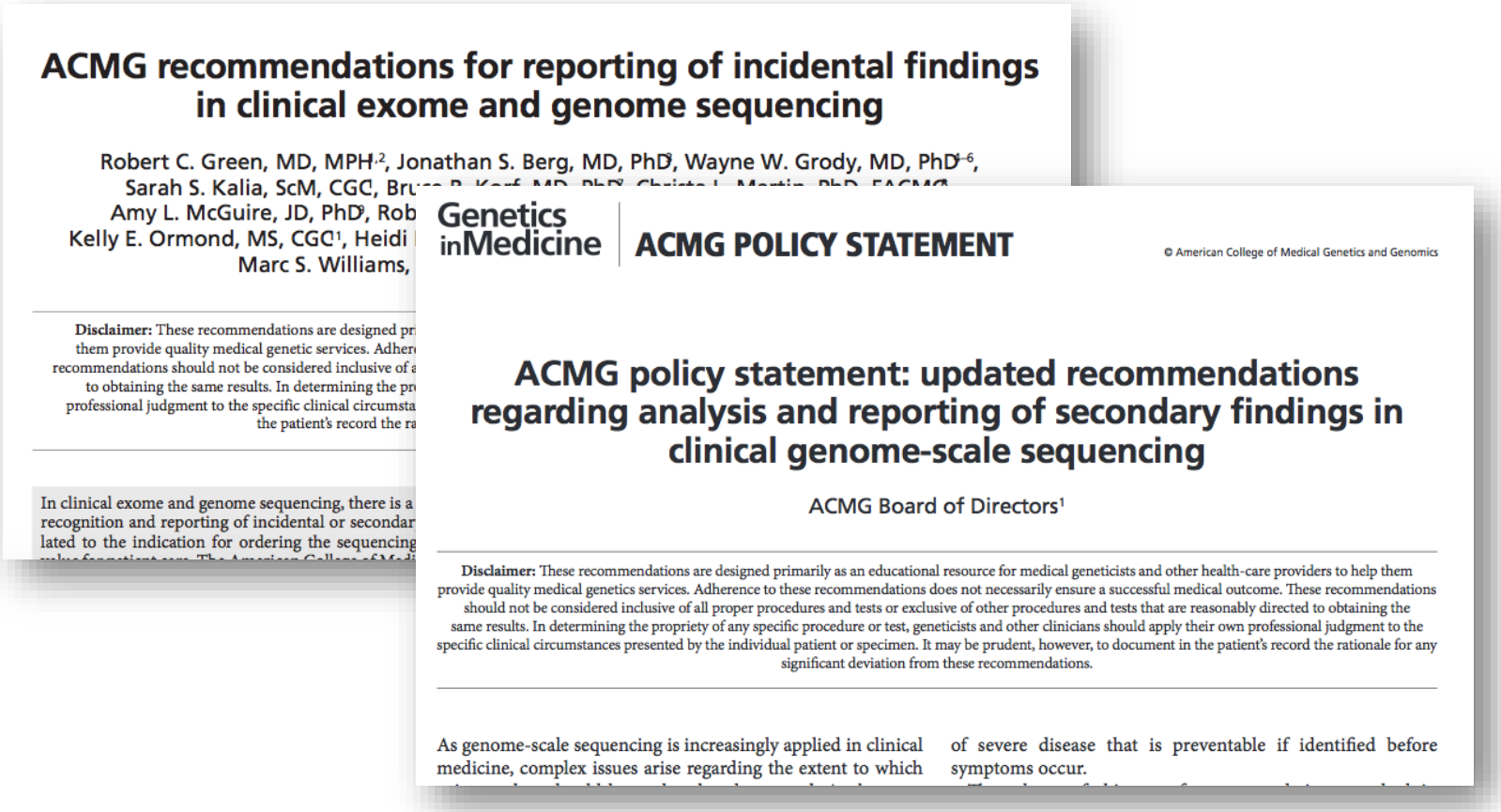
- ACT https://ncats.nih.gov/pubs/features/ctsa-act
- NYC-CDRN http://www.nyccdrn.org
- Observational Health Data Sciences and Informatics (OHDSI) http://www.ohdsi.org
  - >100M patients

Biobanks

- Participants provide open consent for multiple future projects, the details of which cannot be provided at the time of enrollment.
- Future projects will use technologies unimaginable at the time of consent
- Community advisory board is recommended
- Need to consider what to do about return of results and incidental findings


Have a seat Kermit. What I'm about to tell you might come as big shock...

Incidental/Secondary Findings



ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC, Bru… P. Kerf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Rob… Kelly E. Ormond, MS, CGC[11], Heidi … Marc S. Williams, …

Disclaimer: These recommendations are designed pr… them provide quality medical genetic services. Adher… recommendations should not be considered inclusive of … to obtaining the same results. In determining the pr… professional judgment to the specific clinical circumsta… the patient's record the ra…

In clinical exome and genome sequencing, there is a … recognition and reporting of incidental or secondar… lated to the indication for ordering the sequencing …

Genetics inMedicine | **ACMG POLICY STATEMENT**

© American College of Medical Genetics and Genomics

ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing

ACMG Board of Directors[1]

Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other health-care providers to help them provide quality medical genetics services. Adherence to these recommendations does not necessarily ensure a successful medical outcome. These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, geneticists and other clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these recommendations.

As genome-scale sequencing is increasingly applied in clinical medicine, complex issues arise regarding the extent to which … of severe disease that is preventable if identified before symptoms occur.

56 Genes that are **medically actionable with severe but preventable outcomes**, must be reported unless a patient "opts out", any age. Green et al. 2013; ACMG Policy Statement, 2014

Secondary Findings to Report in 1-3% of cases

Hereditary Breast and Ovarian Cancer
Li-Fraumeni Syndrome
Peutz-Jeghers Syndrome
Lynch Syndrome
Familial Adenomatous Polyposis
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas
Von Hippel-Lindau Syndrome
Multiple Endocrine Neoplasia Type 1
Multiple Endocrine Neoplasia Type 2
Familial Medullary Thyroid Cancer
PTEN Hamartoma Tumor Syndrome
Retinoblastoma

Hereditary Paraganglioma- Pheochromocytoma Syndrome
Tuberous Sclerosis Complex
WT1-related Wilms Tumor
Neurofibromatosis Type 2
Ehlers-Danlos Syndrome, vascular type
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections
Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy
Catecholaminergic Polymorphic Ventricular Tachycardia
Arrhythmogenic Right-Ventricular Cardiomyopathy
Romano-Ward Long QT Syndrome Types 1, 2, and 3, Brugada Syndrome
Familial Hypercholesterolemia
Malignant Hyperthermia Susceptibility

Green et al. Genet Med. 2013

JAMA The Journal of the American Medical Association

VIEWPOINT

Return of Secondary Genomic Findings vs Patient Autonomy
Implications for Medical Care

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Viewpoints
pages 365 and 367

In April 2013, the American College of Medical Genetics (ACMG) recommended that clinical laboratories conducting whole genome sequencing (WGS) and whole exome sequencing (WES) for specific clinical indications should also analyze and report any mutations identified from a list of 57 genes considered medically actionable, regardless of whether patients wish to receive the results.[1] These recommendations have sparked a heated debate with profound implications for countless physicians and their patients.

The use of exome sequencing is rapidly increasing in clinical care. Pediatricians are using this tool to assist in diagnosing rare conditions. Oncologists are performing genomic analysis on an increasing number of patients, comparing tumor and normal cells to identify somatic cell mutations that can guide selection of therapy. In the not-too-distant future, such sequencing may be incorporated even more commonly into patient care.

Yet, in interrogating the genome for mutations causing patients' disease, laboratories generate data on other genes unrelated to the indication for testing. With some additional effort, laboratories can evaluate genes that confer increased risk for conditions like breast cancer, colon cancer, aortic rupture, and cardiac conditions that can cause sudden death, for which preventive interventions are available. The ACMG argues that laboratories have a fiduciary duty to seek and return such results for the 57 genes on its list. The guidelines suggest that the laboratory should report these results to the physician, who can then determine whether to convey the results to the patient. However, once such information is in the medical record, to believe that a physician would or could withhold such information from a patient appears unrealistic.

Identification of mutations in these genes[2] is not trivial, given the multitude of errors in the scientific literature about the pathogenicity of many genetic variants, the inexact science of predicting pathogenicity computationally, and the inability to perform the necessive medical screening (eg, magnetic resonance imaging and echocardiograms) or unwarranted procedures such as prophylactic mastectomies.

Moreover, profound disagreements have arisen over whether mutations in these 57 genes should be reported to all patients, regardless of patient preferences or age. Critics have argued[3] that patient autonomy should be respected by allowing patients to choose whether to receive these secondary findings. Whereas proponents claim that the ACMG recommendations still give patients the choice to undergo exome sequencing or not, opponents counter that patients may need testing for diagnosis and treatment of their conditions, but simply not wish to be tested for these other conditions. Currently, many well-informed individuals with known family histories of cancer syndromes, such as hereditary breast and ovarian cancer (*BRCA1* and *BRCA2*) and Li-Fraumeni syndrome (*TP53*), choose to forgo or defer genetic testing, given that disease manifestations and timing cannot be predicted. Additionally, identification of some mutations (eg, hereditary breast and ovarian cancer) has led to difficulty obtaining life insurance.[4] Furthermore, in some communities such as certain Orthodox Jewish groups, identification of a mutation can severely stigmatize patients and their families.

Additional considerations emerge when the patients are children. For most of the conditions on the list of 57 genes, the mutations are incompletely penetrant and many will not manifest until adulthood. Harm may ensue from identifying children as at-risk during formative critical periods of childhood development when identity is significantly shaped by parental perceptions and attitudes. The new ACMG guidelines contradict the organization's prior guidelines for genetic testing in children formulated with the American Academy of Pediatrics, which recommended against predictive genetic testing in minors for adult-onset conditions that are not medically actionable before adulthood.[5,6] The earlier guidelines suggested that children should be allowed to

JAMA The Journal of the American Medical Association

VIEWPOINT

Mandatory Extended Searches in All Genome Sequencing
"Incidental Findings," Patient Autonomy, and Shared Decision Making

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Institute for Bioethics, Health Policy and Law, University of Louisville School of Medicine, Louisville, Kentucky.

Ellen Wright Clayton, MD, JD
Center for Biomedical Ethics and Society, Vanderbilt University, Nashville, Tennessee.

Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)? **—No.**

An incidental finding occurs when a medical test or procedure directed at one condition unexpectedly reveals a separate finding. An example would be when a radiologist notices a chest mass on abdominal computed tomography. By contrast, the American College of Medical Genetics and Genomics (ACMG) statement proposes that whenever genome sequencing is ordered in the clinical setting, laboratories have a mandatory duty to analyze 57 genes (revised to 56 genes) and to report the results to the clinicians and patients, regardless of the patient's age or medical condition.[1] Any positive findings from these additional analyses are hardly incidental; they are the results of a new recomchemotherapy (eg, tamoxifen) or surgery to reduce their risk of developing cancer. All of these recommendations have health risks of their own: radiation exposure from mammograms, increased risk of thrombophlebitis from the medication, and operative and postoperative complications from surgery as well as the psychosocial costs of perceiving oneself as high risk. As the US Preventive Services Task Force reaffirmed in its 2013 draft update on "Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer," these interventions may cause more harm than good when offered and used by women who are less likely to develop disease.[5]

In some ways, mandatory testing in genomic testing/sequencing beyond the scope of the original request more closely resembles the experience with mandatory expanded newborn screening (NBS) than

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VIEWPOINT

Reporting Genomic Sequencing Results to Ordering Clinicians
Incidental, but Not Exceptional

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Leslie G. Biesecker, MD
Genetic Disease

Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)?—**Yes**.

The use of genomic sequencing in medicine is increasing substantially as this technology becomes less expensive and of demonstrated diagnostic utility.[1,2] Potentially clinically relevant incidental findings from clinical exome or genome sequencing (hereafter referred to as genomic sequencing) will arise whenever an individual undergoes genomic sequencing. There is a great deal of controversy regarding how such findings should be addressed by clinical sequencing laboratories because many possible findings are of medical interest and processes for genomic testing and interpretation are not yet standardized. To date, the traditions of genetic testing and reporting have exceptionalized all genetic risk information as potentially dangerous to the well-being of patients. This tradition, in the era of genome sequencing, must be reconsidered.

chest x-ray for the evaluation of a possible rib fracture, he or she has been trained to perform a systematic review of the film, reporting any abnormalities that rise to an established professional standard, regardless of the indication for the study.[7] Importantly, radiologists are specifically trained neither to report every conceivable finding, nor to stop after "satisfaction of search"[8] reveals an indicated finding. Rather radiologists use professional standards to assess and report a subset of unexpected findings that are likely to be medically important. Even though such findings are not always clinically useful, depriving clinicians and patients of these additional findings would not be in the best interest of patient care. In medicine, the search for, and discovery of low-probability, incidental findings by trained health care professionals is not a specified test to which a patient can consent or refuse, but is a process inherent to the performance of good medical care.

The ACMG recommendations have been criticized

GINA and Health Insurance

(effective May 21, 2009)

- Health insurers (Group, Individual, Medicare, Medicaid) may not require individuals to provide their *genetic information* or the genetic information of *family members* to the insurer for eligibility, coverage, underwriting, or premium-setting decisions
- Health insurers may not use genetic information either collected with intent, or incidentally, to make enrollment or coverage decisions
- Health insurers may not request or require that an individual or an individual's family member undergo a genetic test
- Genetic information cannot be used as a preexisting condition

GINA and Health Insurance

(effective May 21, 2009)

- GINA does not protect genetic discrimination in life insurance, disability insurance or long-term-care insurance

Genetic Information and Legal System

- Criminal justice system and ability to implicate individuals in crimes (themselves and their family members)
- Paternity
- Lawsuits for responsibility for bad medical outcomes

What to do about return of results? Is there an ethical duty to rescue?

- Many researchers have old samples with broad consent that did not specify return of any results
- More recent consents allow for preferences for return of results (most participants want results and want all of them), but do not specify types of results to be returned
- Need to consider what to do for deceased patients
- Some studies included minors and now trying to reconsent at the age of majority
  - Children' right to an open future versus the "best interest of the child"

ARTICLE

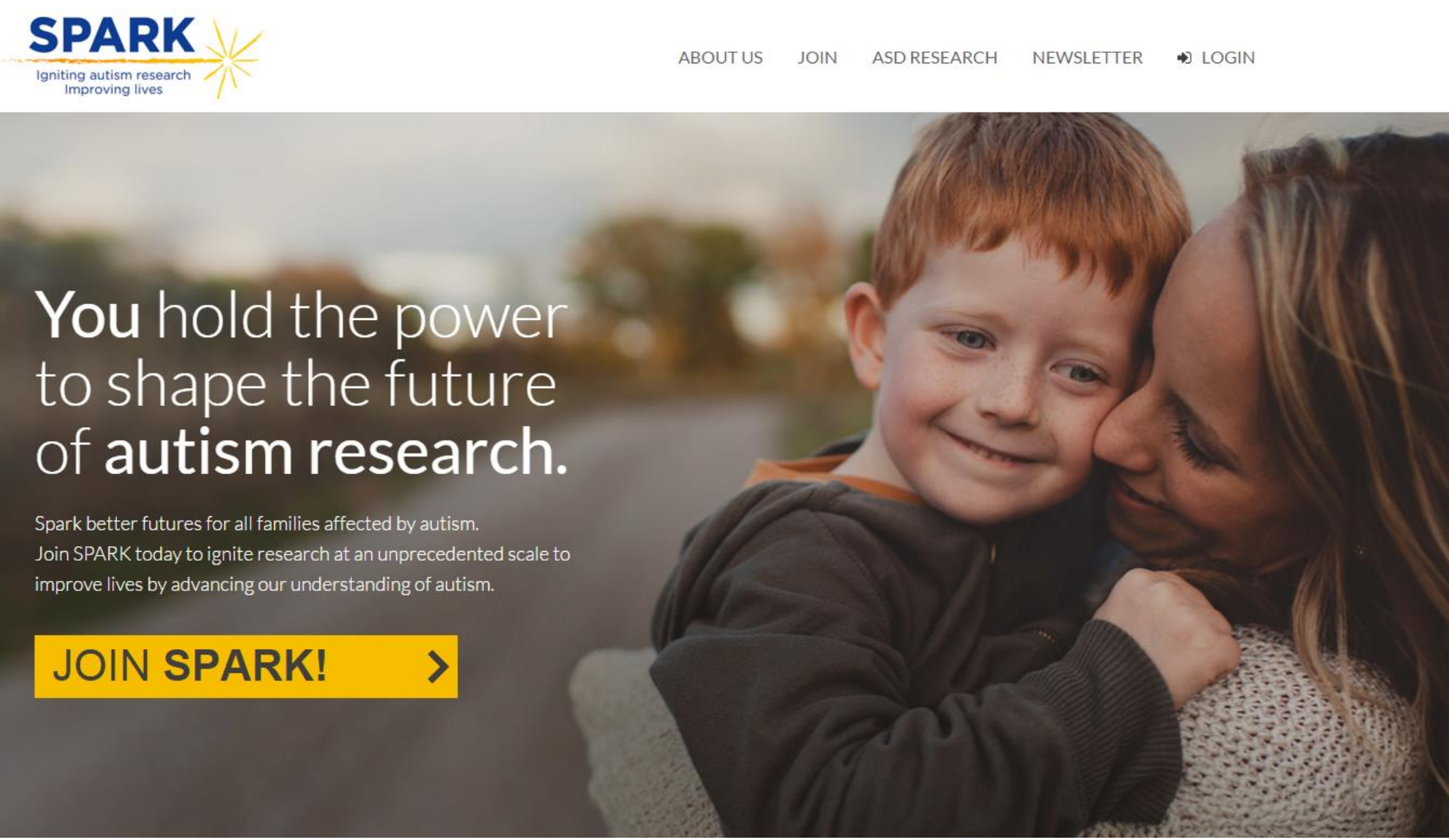
Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between

Gail P. Jarvik,[1,2,*] Laura M. Amendola,[1] Jonathan S. Berg,[3] Kyle Brothers,[4,5] Ellen W. Clayton,[6] Wendy Chung,[7] Barbara J. Evans,[8] James P. Evans,[3] Stephanie M. Fullerton,[9] Carlos J. Gallego,[1] Nanibaa' A. Garrison,[6] Stacy W. Gray,[10,11] Ingrid A. Holm,[12,13,14] Iftikhar J. Kullo,[15] Lisa Soleymani Lehmann,[10] Cathy McCarty,[16] Cynthia A. Prows,[17] Heidi L. Rehm,[10] Richard R. Sharp,[18] Joseph Salama,[1] Saskia Sanderson,[19] Sara L. Van Driest,[6] Marc S. Williams,[20] Susan M. Wolf,[21] Wendy A. Wolf,[12,14] eMERGE Act-ROR Committee and CERC Committee, CSER Act-ROR Working Group, and Wylie Burke[9]

AJHG. Vol 94: 6. p818–826, 5 June 2014

International Studies-special considerations

- Global diversity is important for genomic studies
- Policies differ across countries about policies for return of individual research results
- Ability to move biospecimens internationally may be constrained
- Ability to share data may be constrained, especially since genomic data can be identifying
- HUGO: research samples obtained with consent may be used for other research if there is general notification of such a policy, the participant has not objected, and the sample used by the researcher has been coded or anonymized



SPARKforAutism.org

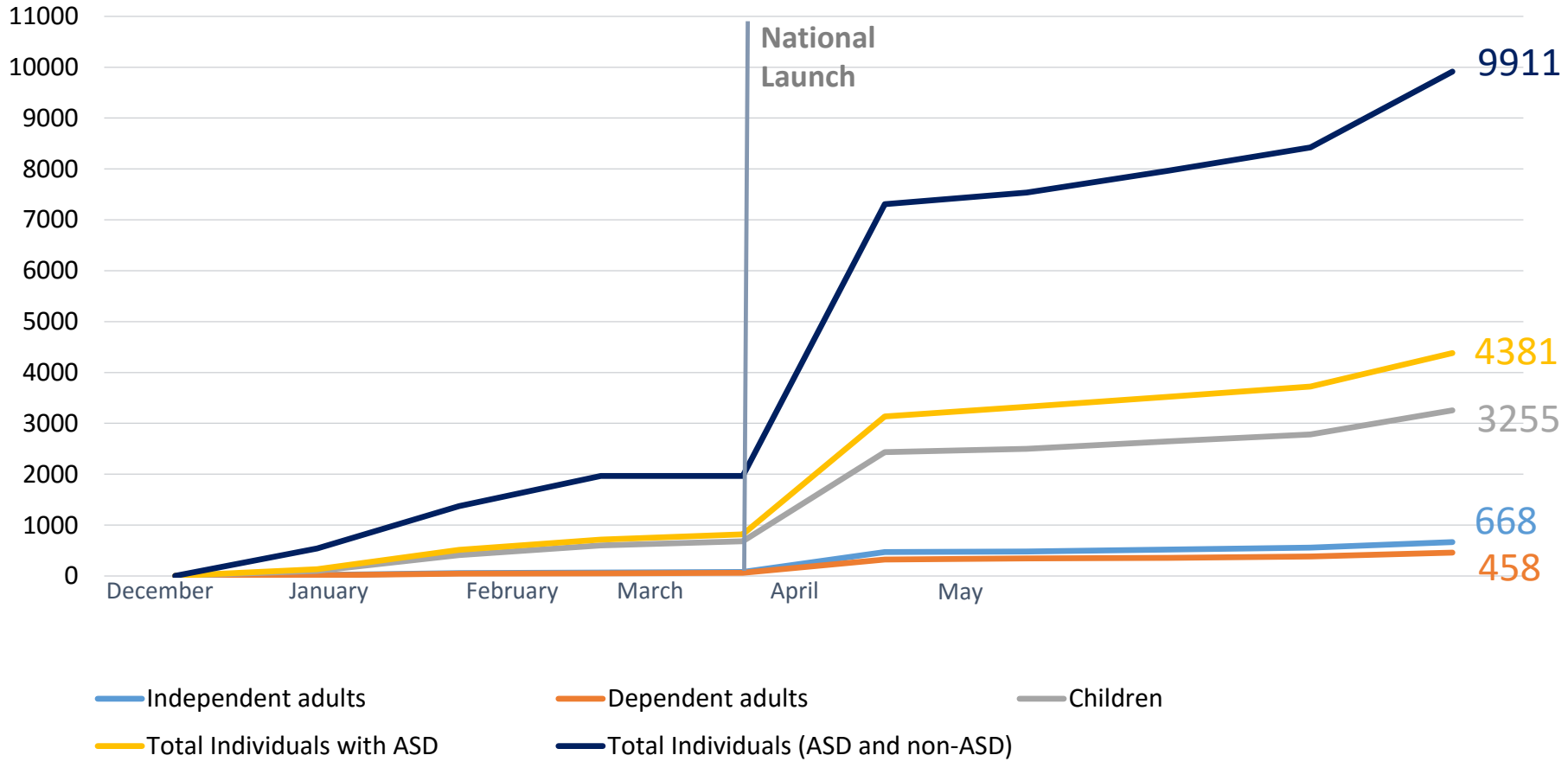
SPARK: Simons Foundation Powering Autism Research through Knowledge

To recruit, engage, and retain 50,000 individuals with ASD and their biological family members to:

- Identify causes of ASD
- Accelerate clinical research
- Enable genotype-driven research
- Accelerate effective treatments
- Create a culture of citizen scientists

SPARKforAutism.org

Individuals Consented to Share Genetic Data



SPARK Data Access

- **Single central IRB**
- **SPARK genetic and behavioral data available to research community as it is generated**
- **Data releases quarterly starting in 2016**
- **Ability to invite participants to research studies online or in person**

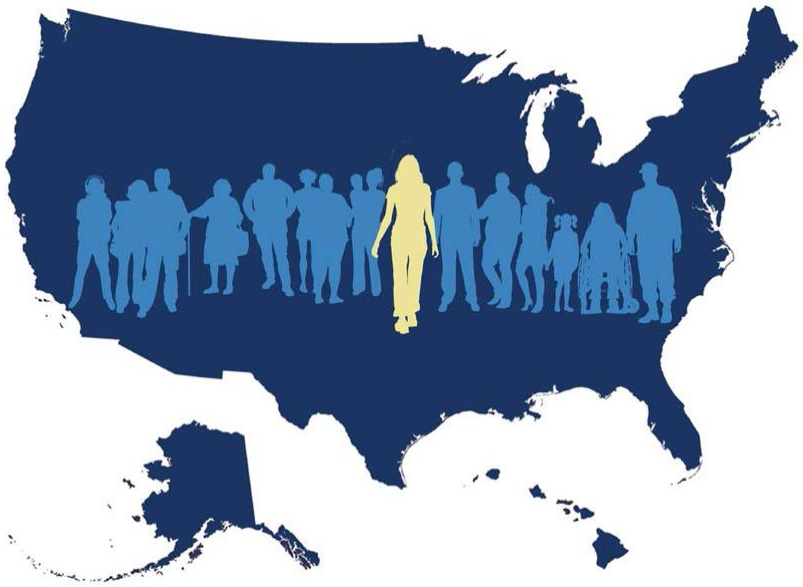
SPARKforAutism.org

Novel clinical outcome measures for ASD

- Apps for report daily behaviors
- Biosensors for real time data collection
- Recording speech
- Recording videos of behaviors

Longer-term goal: The Precision Medicine Initiative Cohort Program

- PMI Cohort Program (PMI-CP) will build a **longitudinal national research cohort of ≥1 million of American volunteers** that will provide the platform for expanding our knowledge of precision medicine approaches.
- The PMI cohort will provide the information needed for:
  - Developing quantitative estimates of risk for a range of diseases.
  - Identifying the determinants of safety and efficacy for commonly used therapeutics.
  - Discovering biomarkers that identify individuals with an increased risk of developing common diseases.
  - Using home and mobile health (mHealth) technologies to correlate body measurements and environmental exposures with health outcomes.
  - Determining the clinical impact of loss-of-function mutations.
  - Enrolling PMI cohort participants in clinical trials of targeted therapies.



"The PMI cohort program, by enrolling and studying one million or more participants in the U.S., will comprise an accessible resource for researchers and participants to work in partnership to accelerate our understanding of health and disease."

GeneDx : Where Rare is common

At the forefront of genetic testing with >700 genetic tests with global presence; most rare / ultra-rare tests offered by any laboratory in the world

Established first-ever commercial laboratory to offer clinical next generation sequencing

FY2015 100,000+ patients

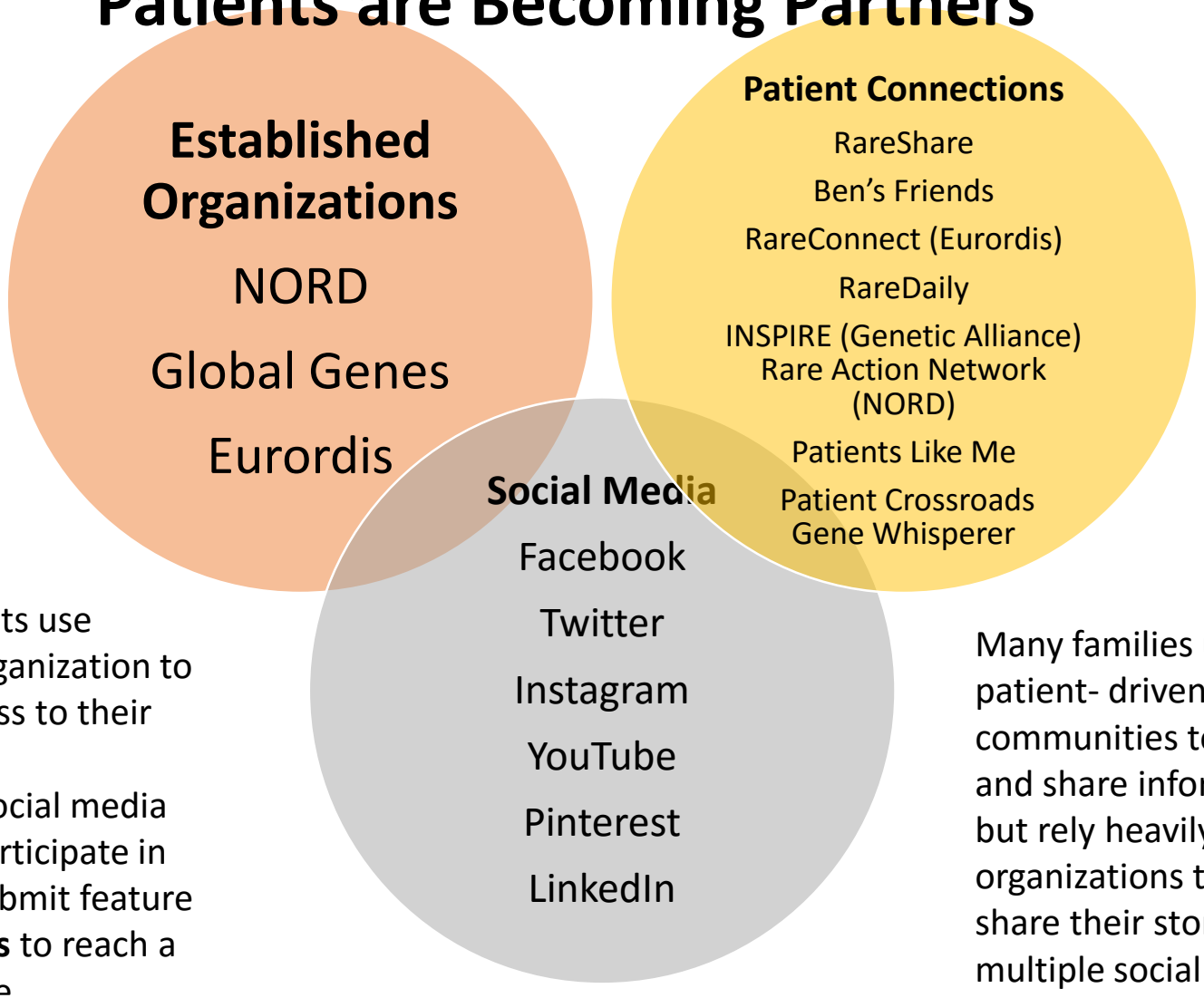
Clinical Genomics Experience

- ✓ **Largest** Rare / Ultra-rare Disease Genetic Repository
- ✓ **>450K** Patients tested
- ✓ **>34K** Exomes Sequenced (over 10,000 Families in largest clinical cohort published)
- ✓ **>75K** Inherited Cancer Tests performed
- ✓ **>45K** Inherited Cardiac Tests performed
- ✓ **>160K** NGS Carrier Screens performed
- ✓ **>7K** Tumor Panels performed

Current Clinical Consents Allow

- De-identified samples may be used for research or for quality improvement laboratory programs

Social Media and the Rare Disease Community
Patients are Becoming Partners



How do patients use established organization to bring awareness to their conditions?
Patients join social media **campaigns**, participate in **events**, and submit feature stories to **blogs** to reach a wider audience.

Many families use patient- driven communities to connect and share information, but rely heavily on larger organizations to help share their stories across multiple social media platforms.

Patient Tools: Facebook Support Groups

Nerissa McCoy Ramsey with Heather Hess Frantz
March 23 at 8:16pm ·

Friends, I have such exciting news! I was just googling Currens condition, and one of the top hits is now Curren's story on the Global Genes blog! They are a huge national rare disease advocacy group, and it is such an honor to be included in their blog.

My strongest passion in life right now to to raise awareness for my son, and to (hopefully) find others in the same situation or (even more hopefully) find individuals interested in researching Curren's gene mutation!

Can you... See More

Curren's Journey: Only the Fourth Person in the World to Be Diagnosed with HIVEP2 Syndrome

My son is two years old, and has seen twelve different doctors in his life. His weekly schedule is jammed packed with 11 hours of therapy – PT, ST, OT, ABA, ITDS – a sea of simplified acronyms for ...

GLOBALGENES.ORG

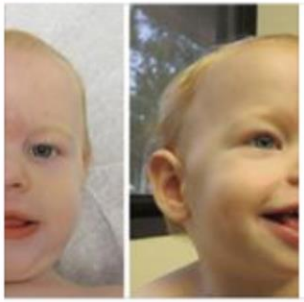
94 6 Comments 30 Share

Share

In the post below, Curren's mother shared the news of a recent **PubMed** alert to inspire hope and increase awareness.

Nerissa McCoy Ramsey ▸ **GRDO (Genetic and Rare Disorders Organisation)**
March 26 at 2:02pm · Melbourne, FL ·

Hi everyone! I have some exiting news that I wanted to share with the group. My son Curren has a mutation in the HIVEP2 gene, located on 6q24.2. Until today, he was one of only 3 known cases of a HIVEP2 loss of function. I got a PubMed alert today that an article was published about HIVEP2, and the article compiles clinical data on 9 known children with HIVEP2 loss of function! My son, Curren is patient number 4 in the publication, and the photos of the patient are of him (he is famous now!) I am really hoping to find the parents of these other kiddos!



Mutations in HIVEP2 are associated with developmental delay, intellectual disability, and...

Human immunodeficiency virus type I enhancer binding protein 2 (HIVEP2) has been previously...

LINK.SPRINGER.COM

8 1 Comment 1 Shar

Like Share

Global Genes, **I love someone rare!** Campaign

Our popular campaign encouraging people to wear the Blue Denim Genes Ribbon™ and their favorite pair of jeans.

Place your order today to receive your Blue Denim Genes Ribbon™ in time for Rare Disease Day!

Find unique, creative, and fun ideas for rare disease day events you can host. Already have an event planned? Share it with our community!

Check our our 2016 RARE World Disease Day Planning Webinar for tips on how to create awareness for your specific rare disease, as well as the rare disease community as a whole!

Learn more about events happening for World Rare Disease Day 2016!

Find out where the Global Genes team will be traveling for World Rare Disease Day 2016!

Changes to the Common Rule

- Consent will be overtly required for any use of biospecimens, even if discarded and de-identified

Current rule	Changes being considered	Rationale for change
Research using existing biospecimens (clinical or from prior research) can be done without consent by stripping the specimens of identifiers.	Reforms would require written consent for research use of biospecimens, even those that have been stripped of identifiers. Consent could be obtained using a standard, short form by which a person could provide open-ended consent for most research uses of a variety of biospecimens (such as all clinical specimens that might be collected at a particular hospital). This change would only apply to biospecimens collected after the effective date of the new rules.	Changing technology in the field of genomics has dramatically increased the amount and nature of information about individuals that can be obtained from their DNA. Surveys indicate a desire on the part of most respondents to be able to decide whether their specimens can be used in research. Providing mechanisms for such control should enhance public trust in biomedical research

Current rule	Changes being considered	Rationale for change
Each site in a study requires IRB review. Although the regulations allow one IRB to carry out the review for multiple sites, it is common for a single study conducted at multiple sites to have many IRBs separately reviewing the study.	For all of the U.S. sites in a multi-site study, the changes propose a single IRB of record.	There is very little evidence that having multiple IRBs review the same study results in enhanced protections for subjects. By diffusing responsibility for that review, it might actually contribute to weakened protections.

Consent: make it meaningful

- With regard to informed consent in general (such as consent to participating in clinical trials), the rules would be significantly tightened to make sure that the process becomes more meaningful.
- Consent forms would no longer be able to be unduly long documents, with the most important information often buried and hard to find.
- They would need to give appropriate details about the research that is most relevant to a person's decision to participate in the study, such as information a reasonable person would want to know, and present that information in a way that highlights the key information.
- Solutions: videos and infographics to simplify concepts

Pharma Needs PR Campaign

- Patients don’t understand what pharma does or how much it costs
  - They feel the price of drugs is too high
- Patients don’t know what happens to their data
  - Increased communication
- Need to support community, partnership, and transparency to build trust
- Engage patients early and keep them engaged
- Benefit of honest brokers

Conclusion

- Write consents broadly
- Make consents meaningful (use videos, infographics)
- Register preferences for data/biospecimens use and return of results at baseline
- Build in the ability to recontact/reconsent/reset preferences
- Include the patients community early and often

LearningGenetics.org

Patient education resource