Speeding genomic medicine to benefit children & families

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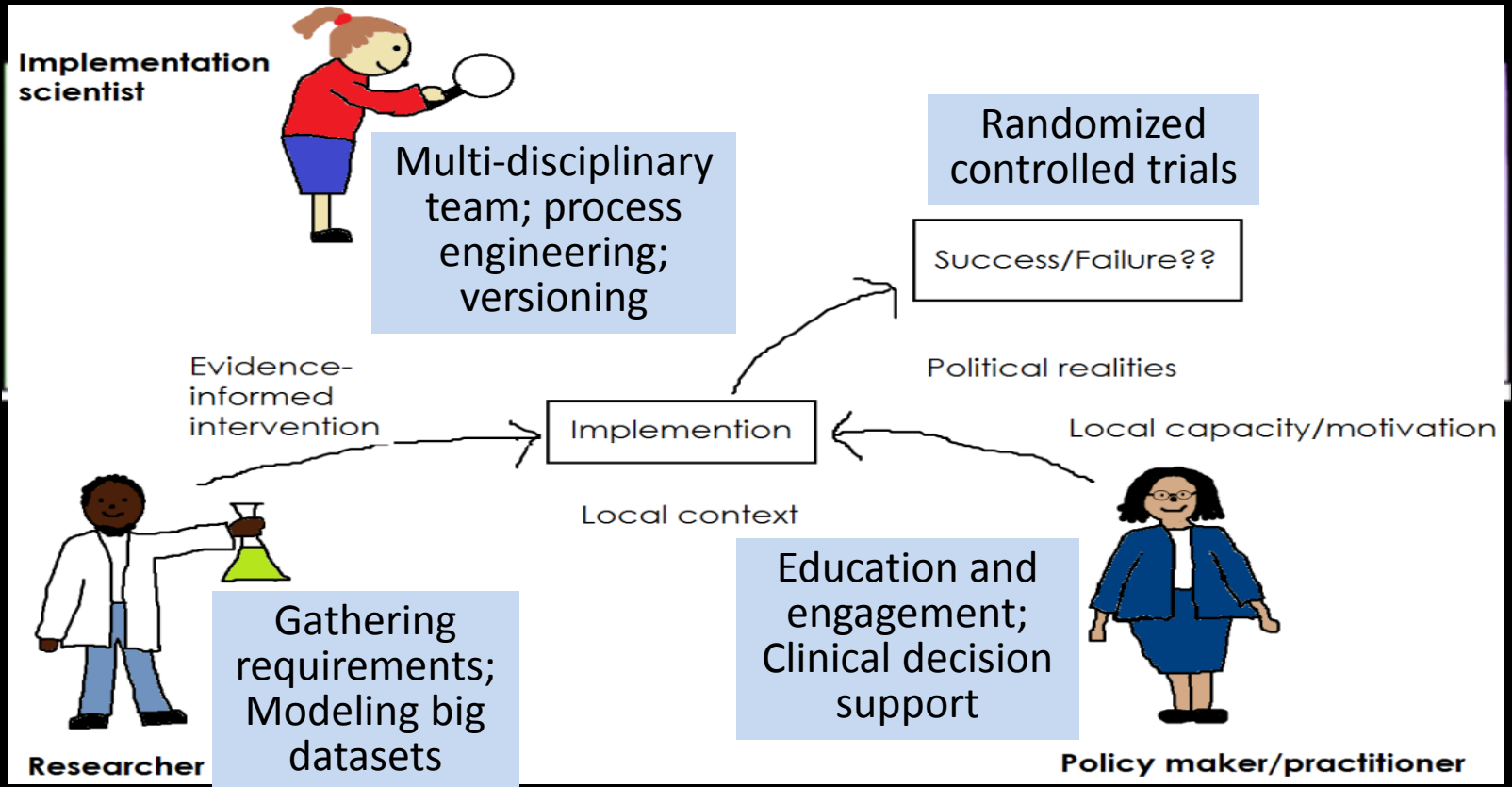
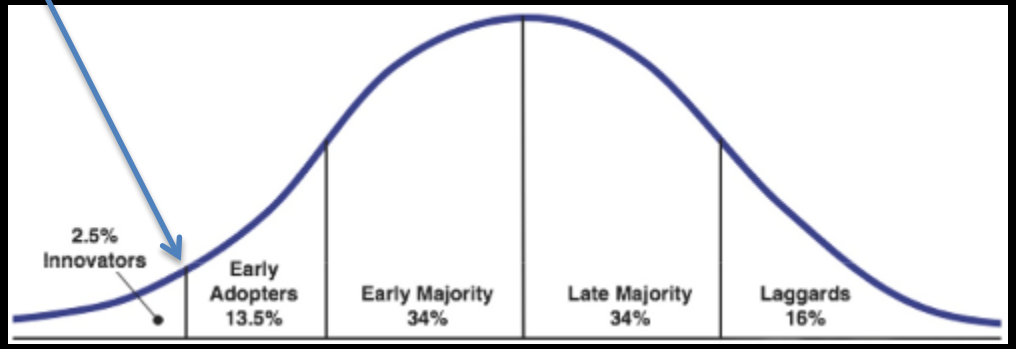
Increased Adoption of Genomic Medicine will require investments in Implementation Science



Adoption of Genomic Medicine Status:



One Homogeneous Setting: Single Gene Diseases

- 22 Level III and IV NICUs; 18,000 infants
- 25 PICUs; 12,000 children

Favorable Economics

Level II	Special care nursery	Infants ≥32 wk/≥1500g with moderate problems; Ventilation <24 hours
Level III	NICU	+ Sustained life support + <32 wks/<1500 g/critical illness
Level IV	Regional NICU	+ Complex surgery + all pediatric subspecialties

2009 Charges for Level II-IV NICUs

- 14% of newborns

Gestational Age	Average Length of Stay (Days)	Average Hospital Charges (Dollars)
All Admissions	13.2	$76,164
<32 weeks	46.2	$280,811
32-33 weeks	20.3	$102,182
34-36 weeks	9.8	$51,083
37-38 weeks	5.9	$37,137
39-41 weeks	4.9	$29,771
42+ weeks	6.5	$47,282

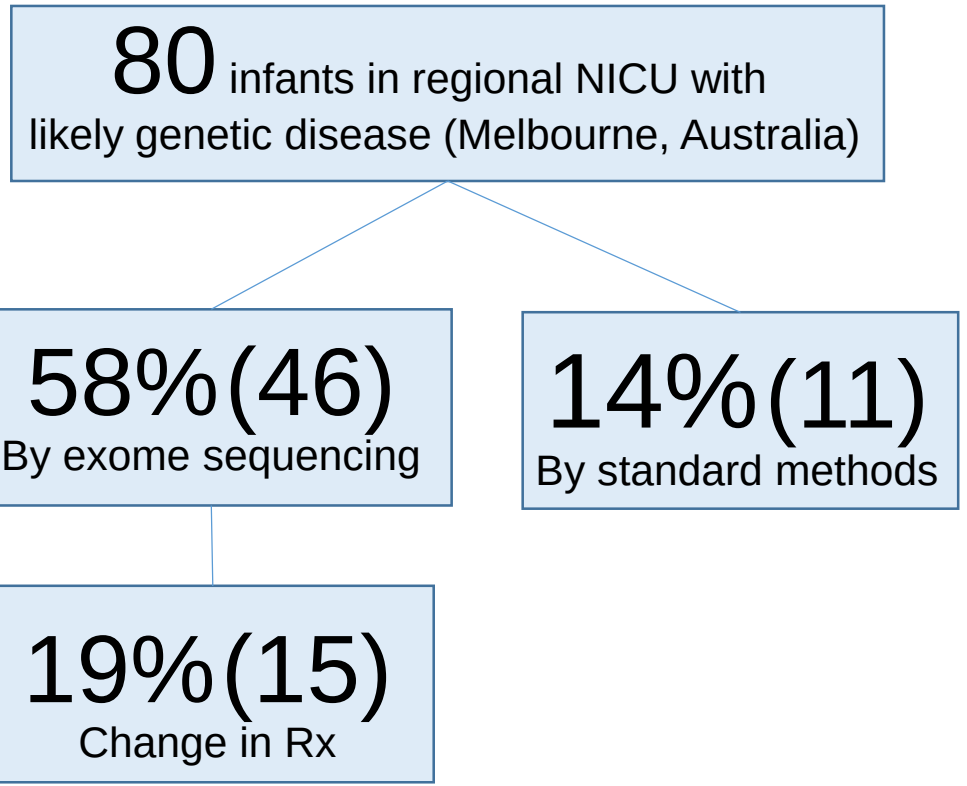
The Data

Neonatal Need for Genomic Medicine

- Leading cause of death in NICU, PICU, infants
- 8000 named diseases; ↑ by 20/month
- Delayed/no diagnosis:
  - Suboptimal outcomes
  - Failure to predict complications
  - Incorrect treatments
  - Prolonged stays
  - Suboptimal candidate selection for interventions: ECMO
  - Inability to choose palliative care track

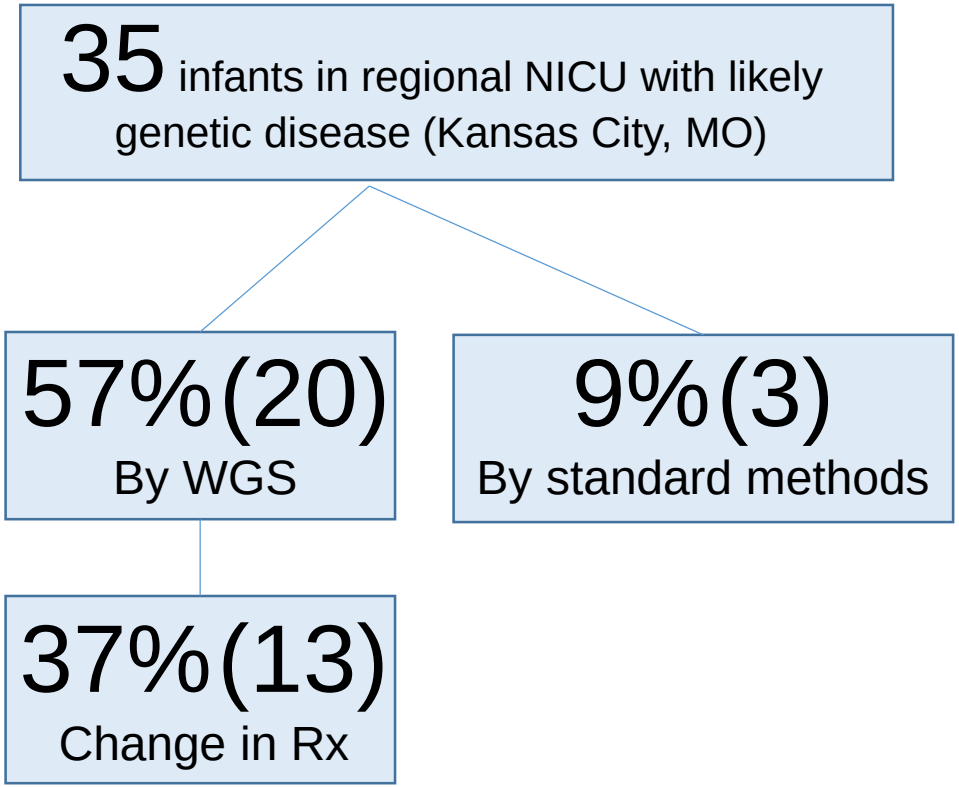
A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders

Stark Z, *et al. Genetics in Medicine* 3/3/2016



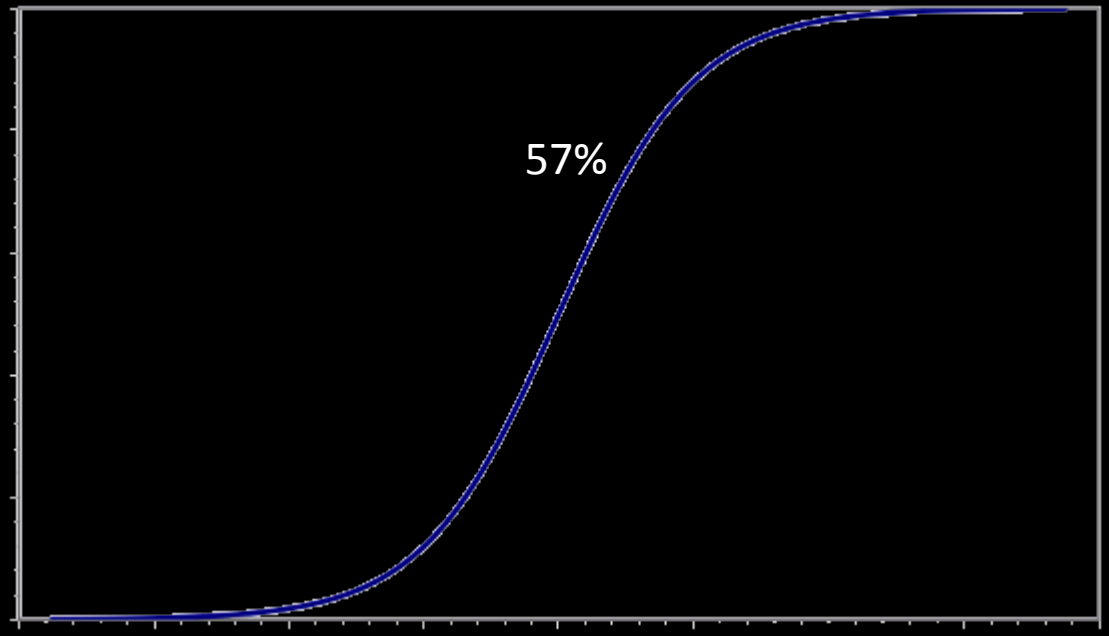
Molecular Diagnosis
But: Median time to Dx ***134 days***

Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings Willig LK, *et al. Science Trans. Med*. April 2015



Molecular Diagnosis
But: Enrollment **26 days**; Dx **23 days**

Diagnostic Yield of WES/WGS

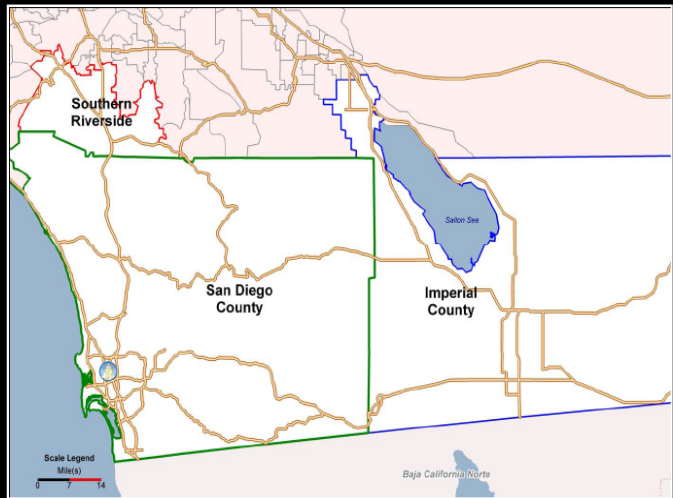


Acute Clinical Utility of Median Day 49 NICU/PICU Molecular Diagnosis

			Est. DOL 7 Dx
Diagnosis Prior to Discharge	37%	Est. QALYs Added	94%
Palliative Care Guidance	**17%**		31%
Life saved	**3%**	**70**	3%
NICU stay ↓ by >1 month	**3%**		34%
Major morbidity avoided	**6%**	**11**	**?**
Genetic Counseling Change	11%		
Medication Change	11%		
Procedure Change	9%		
Diet Change	6%		

Our Perspective

Rady Children's Institute
Genomic Medicine



The Opportunity

Rady Children's Institute
Genomic Medicine

Measurable impact

County	Population 2014	Children with Genetic Diseases	Genome sequences / year	New Diagnoses / year	QALYs saved/ year
San Diego	3,263,431	22,126	8,284	1,327	5,773
SD,Imperial, Riverside, Orange	8,917,308	64,458	24,134	3,866	16,818

The bits we have figured out:
26 Hour Medical Genome Sequencing

1	• Consent, Phlebotomy, Transport
1.5	• DNA Prep & QC
4	• Library Prep & QC
18	• 2 x 101 cycles
0.5	• Bcl to fastq to vcf
0.5	• Vcf Annotation
0.5	• Variant interpretation of genes in differential diagnosis

Scalability of WGS/WES

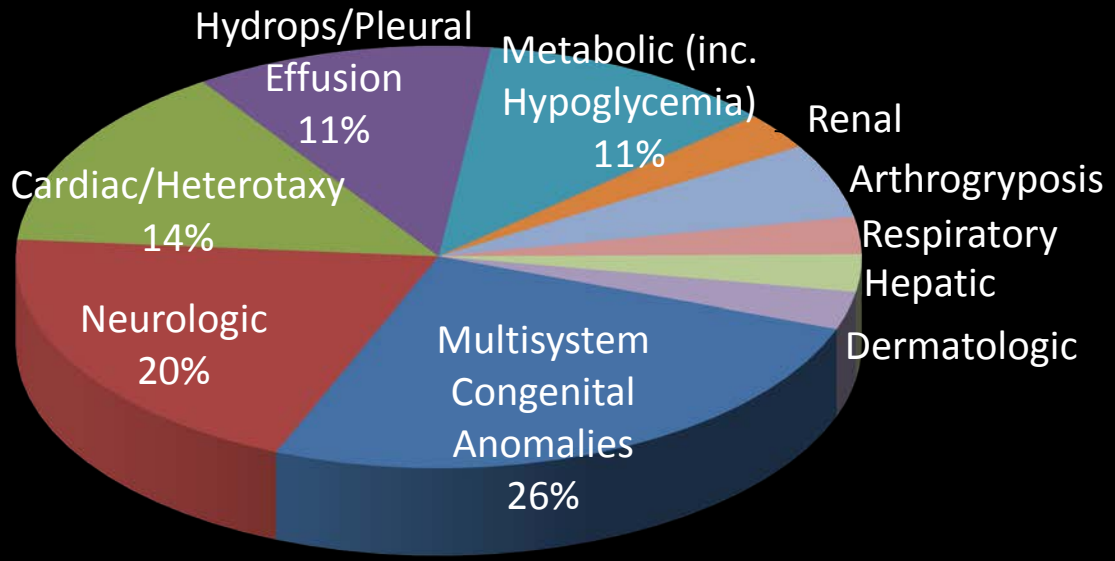
Illumina Sequencer	Max.Families Per Year	Consumable cost per family	Time to result
Modified HiSeq 2500	100	$20,000	18 hours
HiSeq X	600	$2,700	18 days

illumina

The bits we havn’t figured out

Timely Patient Ascertainment

No phenotypic feature associated with higher diagnostic yield



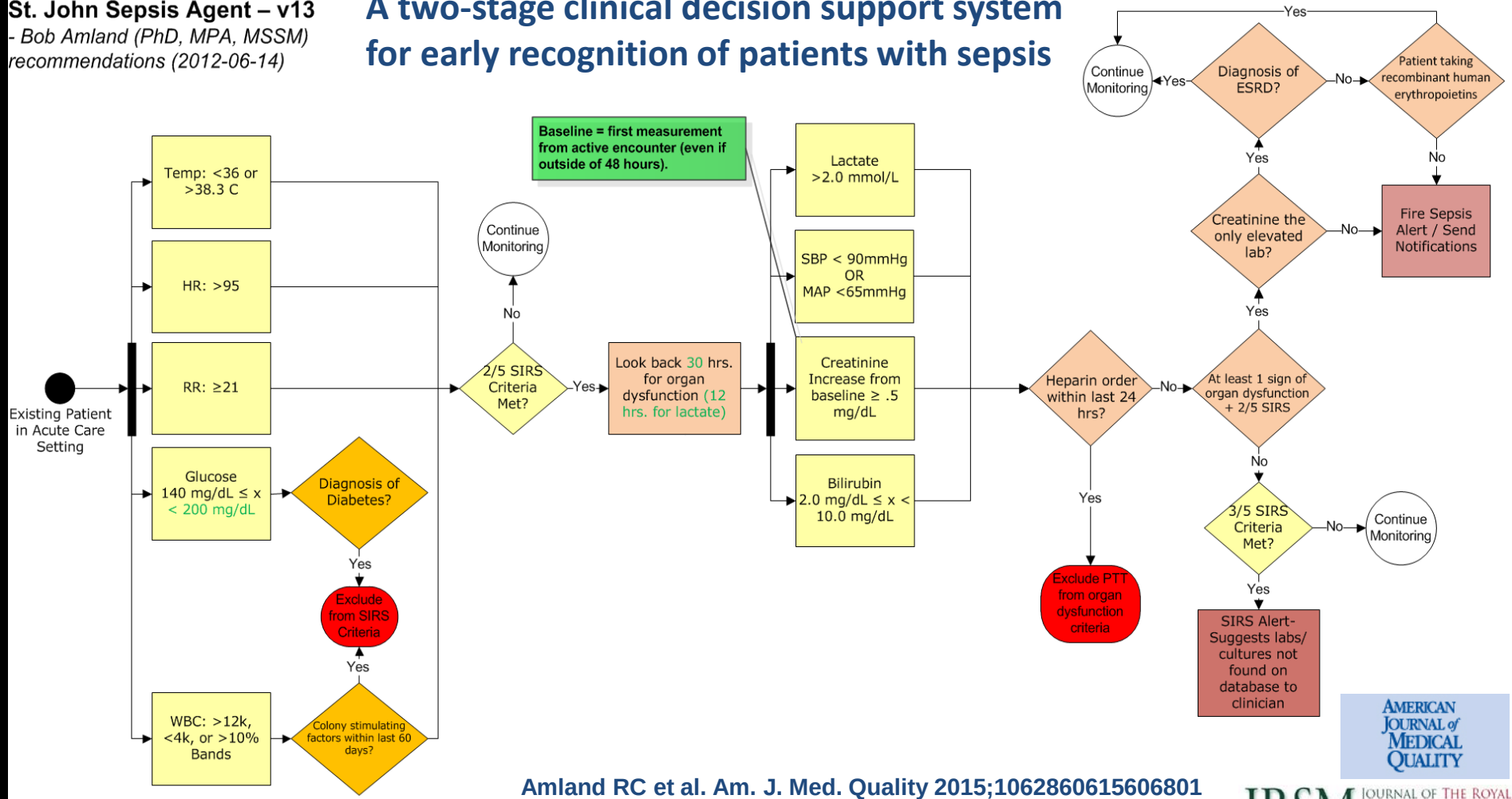
Characteristic	Number (%)	Diagnostic rate
Congenital abnormalities and dysmorphic features	43 (54%)	21/43 (49%)
Neurometabolic disorder	19 (24%)	14/19 (74%)
Skeletal dysplasia	6 (7%)	4/6 (67%)
Eye	3 (4%)	2/3 (67%)
Other (gastrointestinal, renal, immunological)	9 (11%)	5/9 (55%)

Innovation 1

- Automated, dynamic, electronic surveillance system for ascertainment of infants likely to benefit from genome sequencing
  - Data model
  - Algorithm
  - Paramaterize with database

St. John Sepsis Agent – v13
- Bob Amland (PhD, MPA, MSSM)
recommendations (2012-06-14)

A two-stage clinical decision support system for early recognition of patients with sepsis



Amland RC et al. Am. J. Med. Quality 2015;1062860615606801
Amland RC et al. JRSM Open. 2015 6: 2054270415609004

Possible Sev

Sepsis Screening Results

SIRS Criteria
10/22/2014 09:00 HR (120 bpm)
10/22/2014 09:00 Temp (39 degC)
10/22/2014 09:00 RR (25 br/min)
Organ Dysfunction
10/22/2014 09:00 Systolic BP (85 m

Date/Time Provider Notified

10/22/2014 0938

SEVERE SEPSIS Alert

The following information suggests that this patient may have Severe Sepsis.
Click on Screen button (lower left) to complete the Sepsis Screening and Stratification form and treat as clinically appropriate.

If you are not the Attending, Covering Attending, APP or Resident please press the Bypass button below.

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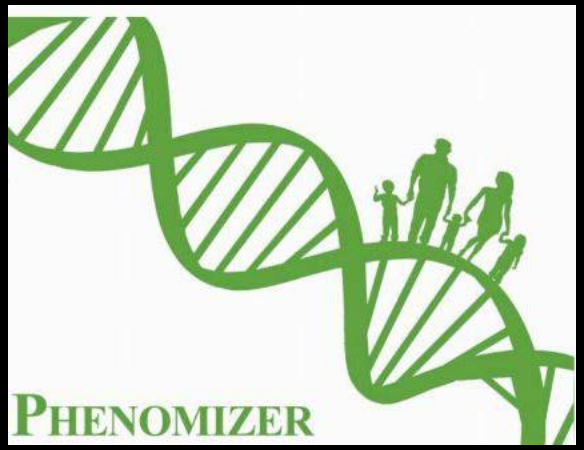
Gap / Challenge 2

- Making a differential diagnosis
  - 916,000 MDs in US, but only 2,300 genetic counselors

Clinical Feature x OMIM Matching



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Automated, dynamic clinical feature extraction from EHR & data-driven models of genetic disease topologies

Gap 3:

The fiscal environment

The $1,000 genome, the $100,000 analysis.

Elaine Mardis, PhD
Washington University,
St. Louis

New variant (mutation) pathogenicity categories

Category	NEW CRITERIA
Pathogenic	1 VS + (1 S or 2 M/Supp) 2S 1S + (3M or 2M+2Supp)
Likely Pathogenic	1 VS/S + 1 M 1 S + (1 M or 2 Supp) 3 M 2 M + 2 Supp 1 M + 4 Supp

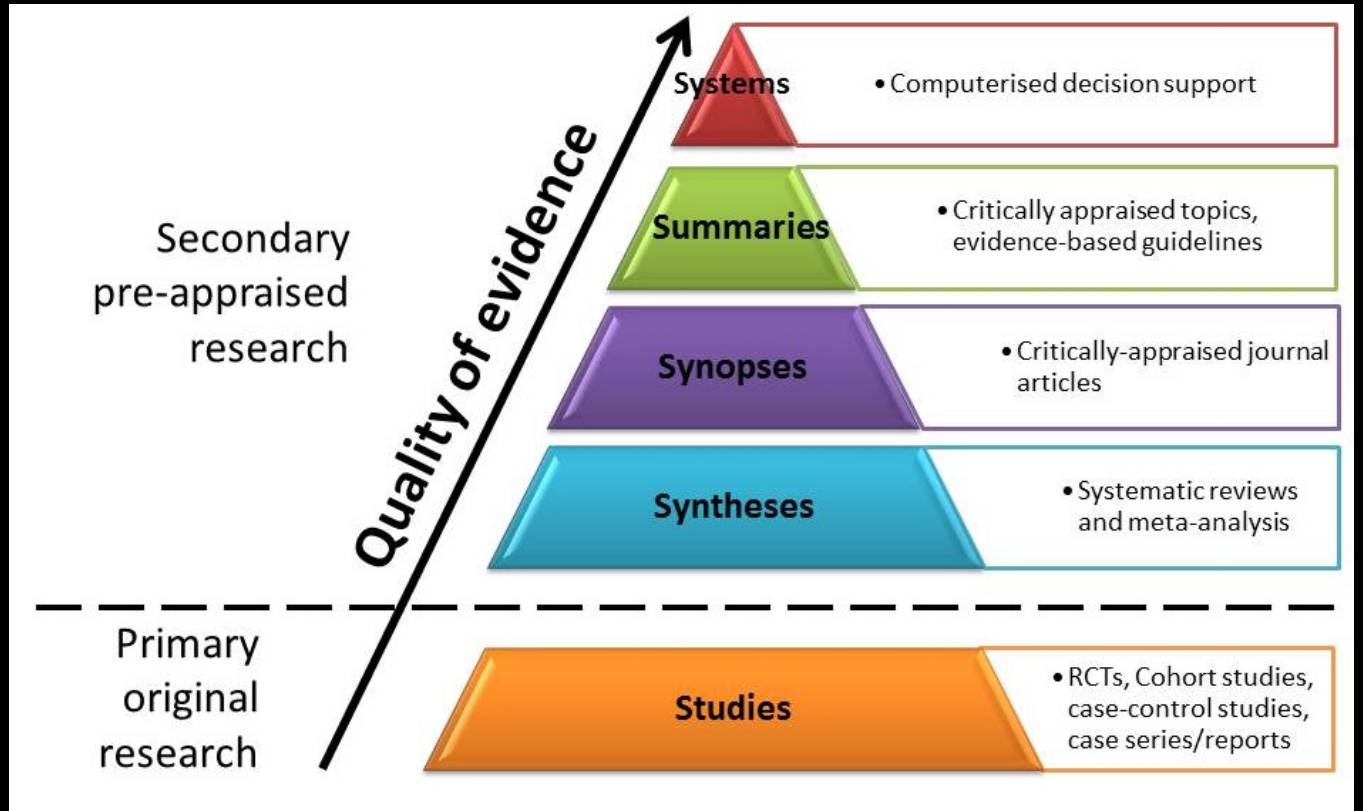
Very Strong	Null variant (nonsense, frameshift, ±1 or 2 splice site position, initiation codon, exon deletion) in gene where LOF known to cause disease
Strong	• Same amino acid change as previously established pathogenic variant • De novo in a patient with the disease and no family history • Functional studies show damaging effect on the gene • Prevalence in affected individuals significantly greater than controls
Moderate	• Located in mutational hot spot/functional domain without benign variation • Extremely low frequency in Exome Sequencing or 1000 Genomes Projects • For recessive disorders, detected in trans with a pathogenic variant • Protein length changed by in-frame indel in nonrepeat region or stop-loss • Novel missense at amino acid where different missense known to be pathogenic • Assumed de novo, but without confirmation of paternity and maternity
Supporting	• Cosegregation with disease in multiple affected family members in gene known to cause disease • Missense variant in gene with low rate of benign missense variants and where missense variants commonly cause disease • Multiple computational tools call deleterious • Phenotype highly specific for disease with single genetic etiology • Reputable source reports as pathogenic, but unpublished

Genet Med. 2015 Mar 5. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of ACMG and AMP. Richards S, et al.

Solution: Automated Variant Curation & Semi-automoated Variant Filtering

Gap 4: Genome reimbursement

Solution: High quality evidence; strong MD support



Challenges	Solutions
Timely patient ascertainment	EHR-driven automated alert system
Genome cost versus timeliness	Moore's law, market forces
Comprehensive differential diagnosis	Automated diff. Dx. SW; EHR data extraction SW
Too few Lab Directors, Med. Geneticists, Genetic Counselors	Targeted education of generalist MDs and NPs; eCDSS
Inadequate reimbursement of genetic tests	Clinical trial evidence; capitated care

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