Technical Desiderata for gCDS: A Reflection on Implementation in eMERGE III

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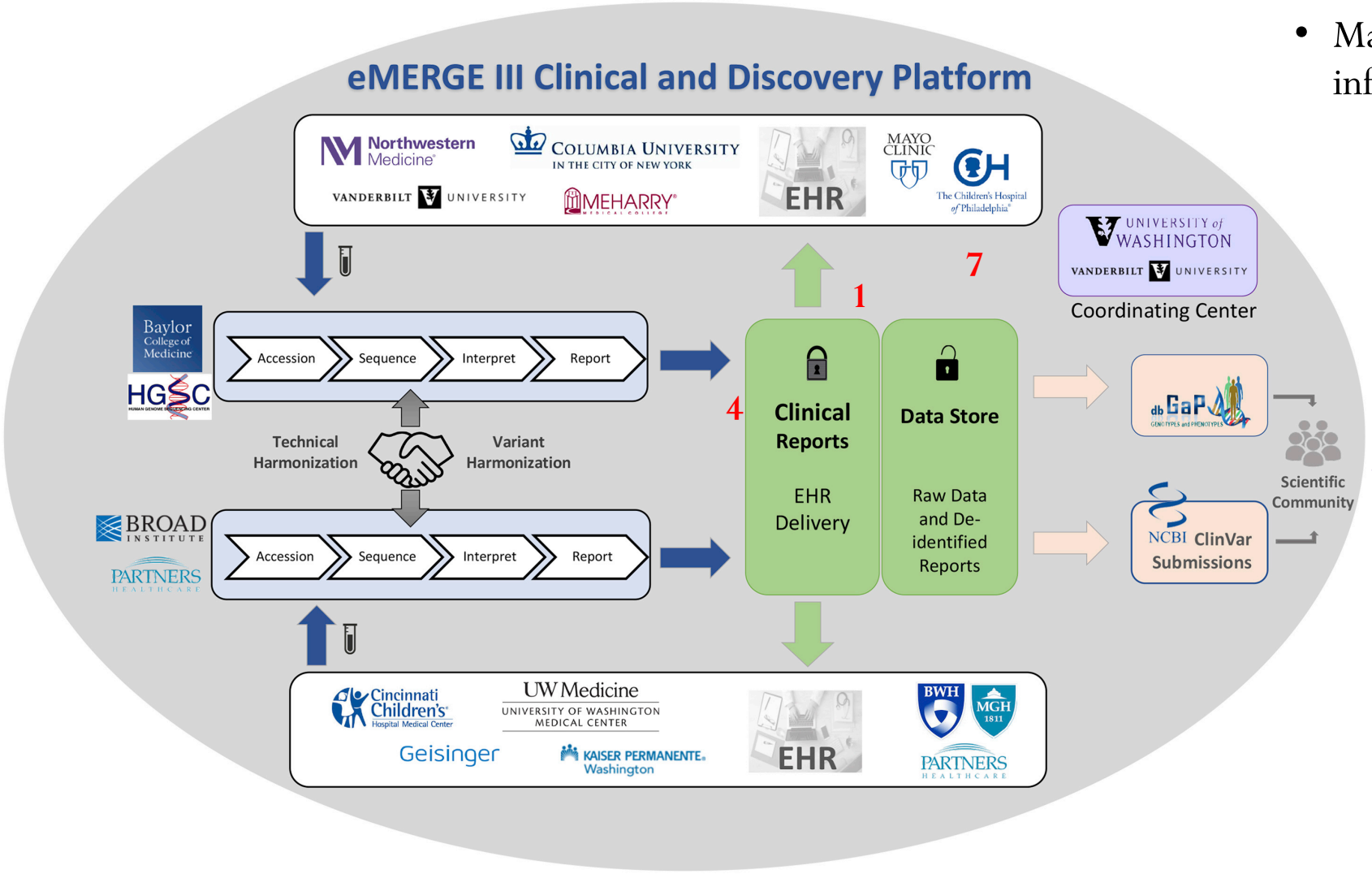
NHGRI Genomic Medicine XIII
February 9, 2021

Topics to cover

- "Progress made in addressing, and identifying remaining barriers described in the technical desiderata for genomic clinical decision support and for the integration of genomic data into the electronic health record."
  - Examples from eMERGE III
- Survey Question: The genomic medicine community will benefit from having a revised technical desiderata
  - Areas to consider from eMERGE III experiences
- "Areas where a research strategy developed by the NHGRI could be useful in achieving the goals described in the desiderata."

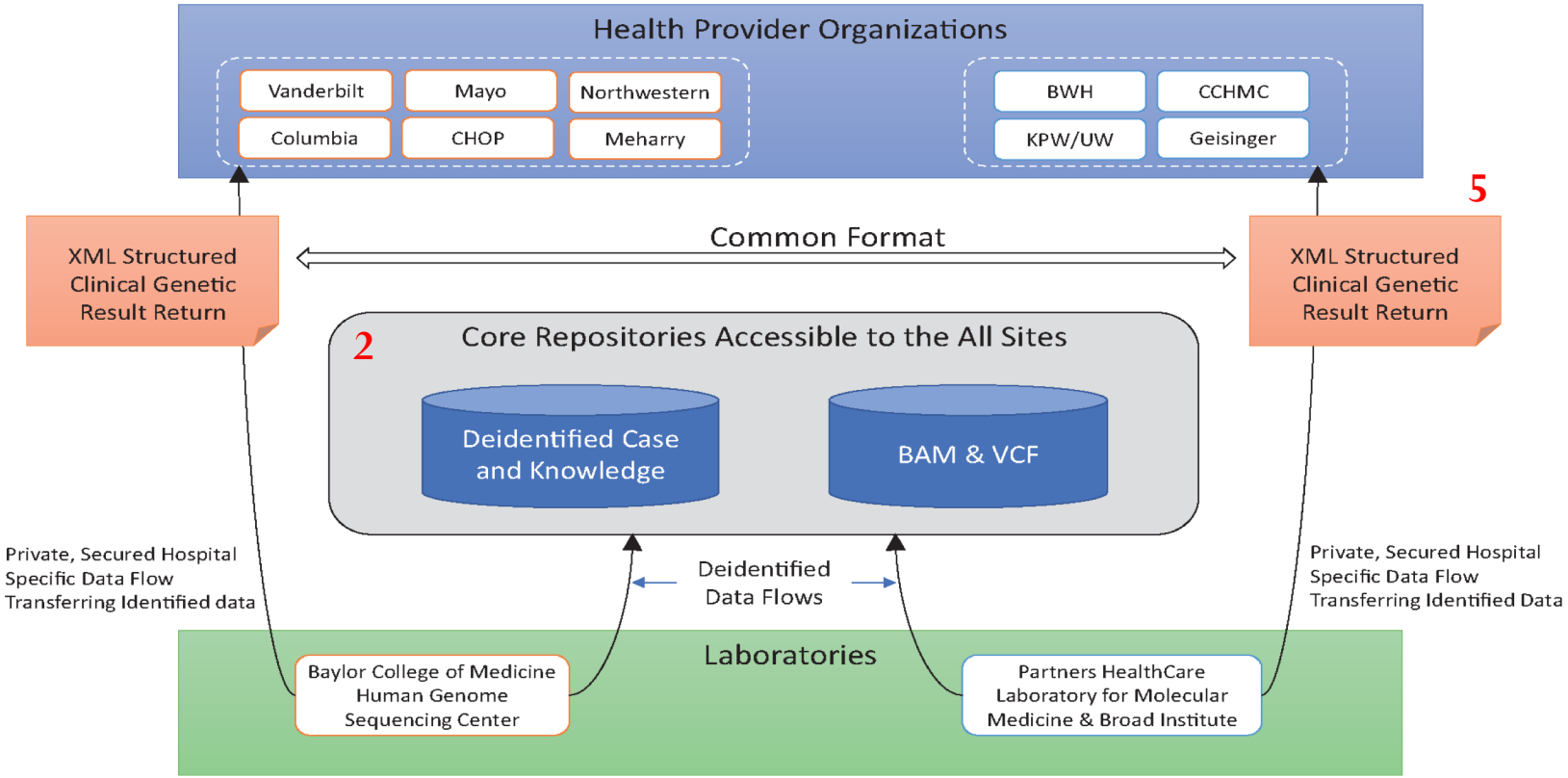
eMERGE III Clinical and Discovery Platform



- Masys et al. desiderata to integrate genomic information within the EHR
  1. Maintain separation of primary molecular observations from the clinical interpretations of those data
  2. Support lossless data compression from primary molecular observations to clinically manageable subsets
  3. Maintain linkage of molecular observations to the laboratory methods used to generate them
  4. Support compact representation of clinically actionable subsets for optimal performance
  5. Simultaneously support human-viewable formats and machine-readable formats in order to facilitate implementation of decision support rules
  6. Anticipate fundamental changes in the understanding of human molecular variation
  7. Support both individual clinical care and discovery science

The eMERGE Consortium. Harmonizing Clinical Sequencing and Interpretation for the eMERGE III Network. AJHG. 2019;105(3):588-605. https://doi.org/10.1016/j.ajhg.2019.07.018

Architecture Supporting Transfer of Genomic Results from the Lab to Health Provider Organizations



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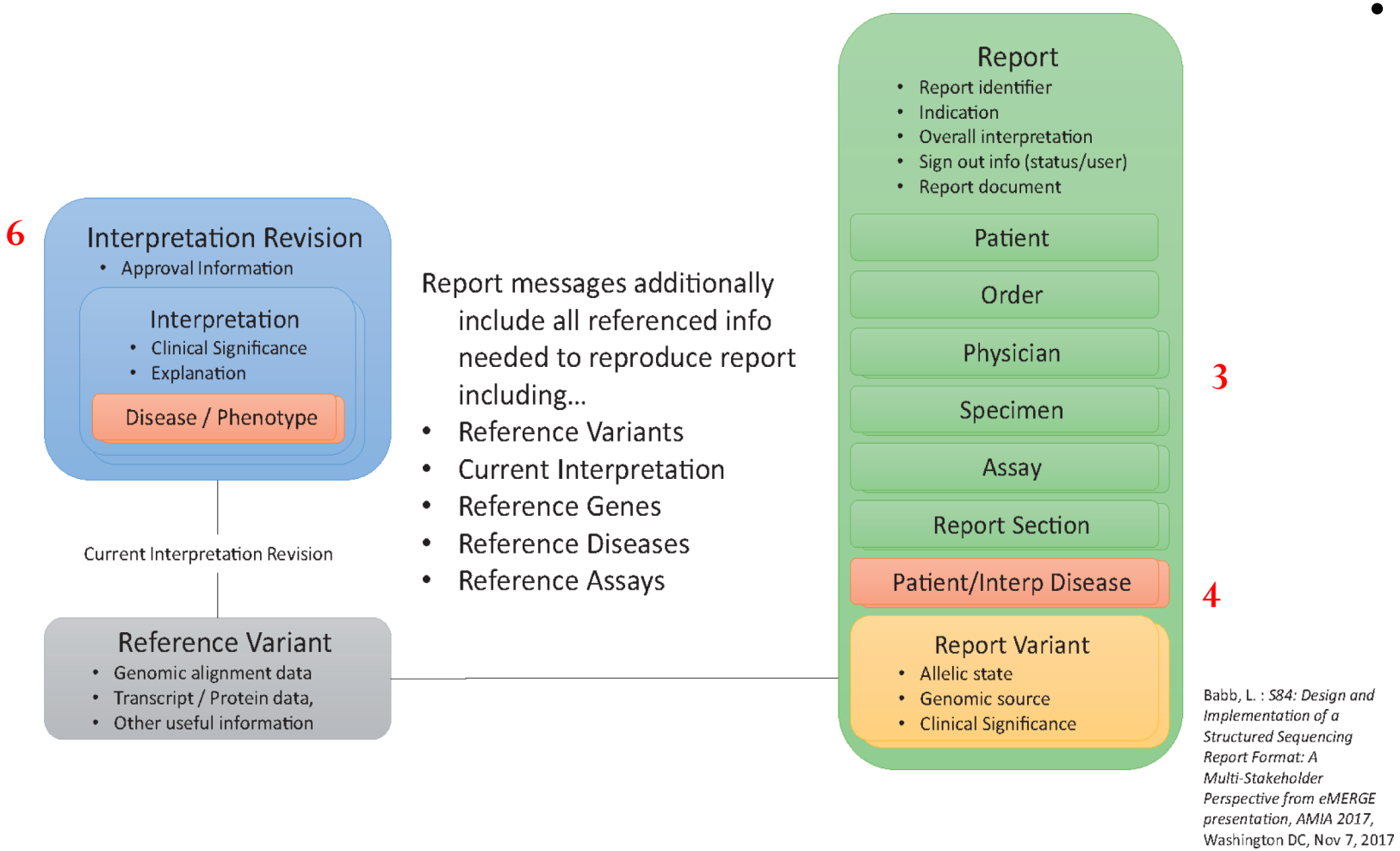
The eMERGE EHRI Working Group. Empowering genomic medicine by establishing critical sequencing result data flows. JAMIA. 2018 Oct;25(10):1375-81. doi.org/10.1093/jamia/ocy051

Structured Genomic Sequencing Report Format



Babb, L. : *S84: Design and Implementation of a Structured Sequencing Report Format: A Multi-Stakeholder Perspective from eMERGE presentation, AMIA 2017,* Washington DC, Nov 7, 2017

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gCDS capabilities enabled by standardized reports and processes

Table 1. Items Harmonized across the Two Sequencing Centers

Item	Challenge	Comments
Collection sites	sample type	agreed to blood[a,b]
	sample quality	minimal quantity specified[a]
	intake formats	standard tables supplied to sites
	phenotypes	not shared unless indication for testing
	patient ID structure	naming conventions
Data delivery	physician clinical reports	11 PDFs, consumable xml structure; GeneInsight
	network access to interpreted variants and de-identified reports	13 GeneInsight de-identified case repository, DNAnexus Commons
	community data sharing	dbGaP and ClinVar submissions
Variant classification	initial harmonization	required harmonization of all medically significant differences observed 5 or more times in tested genes
	ongoing classifications	9 required consensus between labs or elevation to Clinical Annotation WG for network consensus
Report content[a]	consensus content	8 67 genes and 14 SNVs
	site-specific genes and SNVs	see Figure 4 and Table S7
	updates	variant reclassifications provided
	variants and de-identified reports	DNAnexus Commons
	community data sharing	dbGaP and ClinVar submissions
Progress reporting	specimen progress	sequencing and reporting timelines
	aggregate statistic reporting	rates of secondary findings; detection rates for indications

- Welch et al. desiderata to integrate genomic information within CDS capabilities

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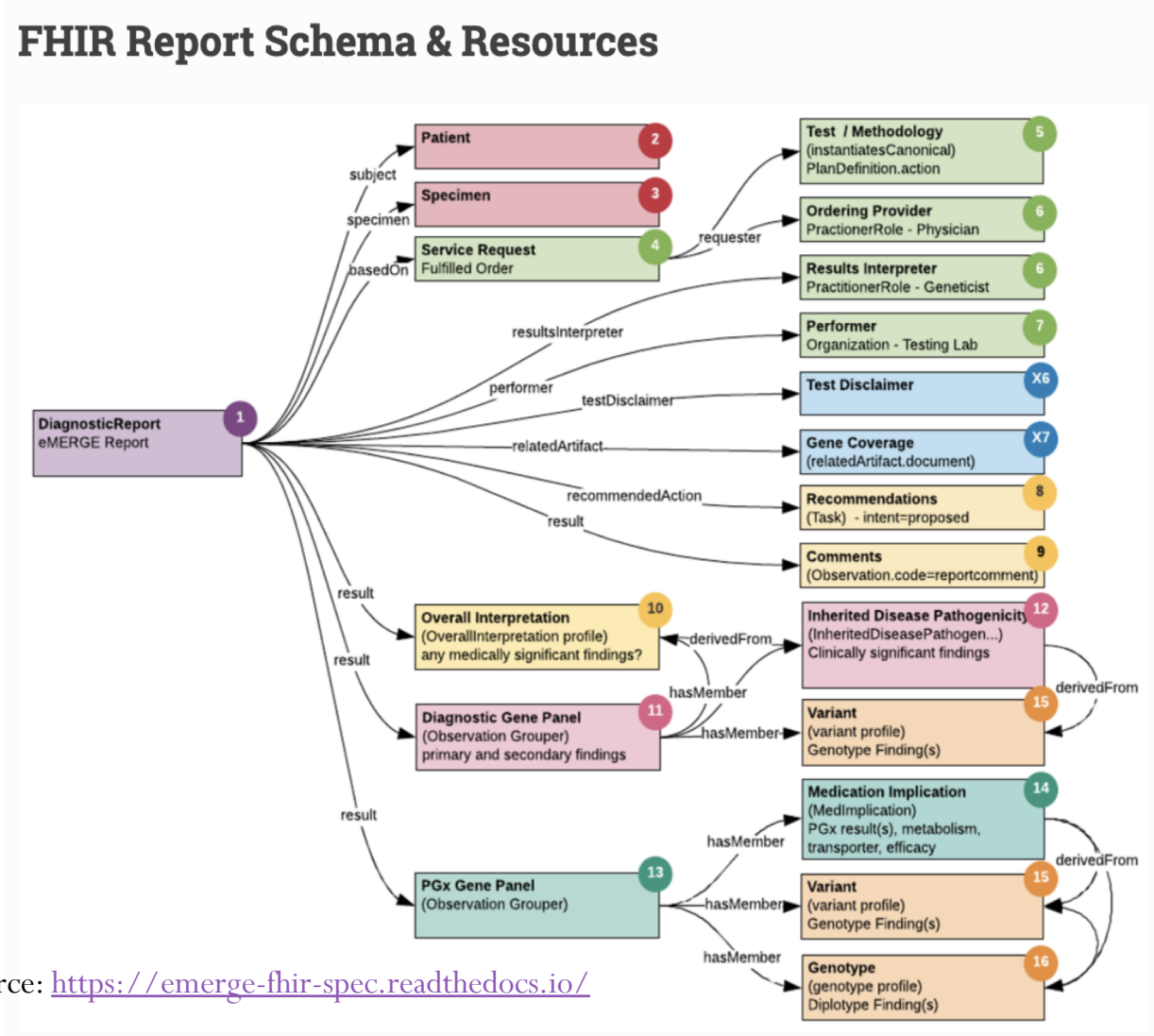
Filling gaps by standardizing report format for data exchange



Source: https://emerge-fhir-spec.readthedocs.io/

- Welch et al. desiderata to integrate genomic information within CDS capabilities
  8. CDS knowledge must have the potential to incorporate multiple genes and clinical information
  9. Keep CDS knowledge separate from variant classification
  10. *CDS knowledge must have the capacity to support multiple EHR platforms with various data representations with minimal modification*
  11. Support a large number of gene variants while simplifying the CDS knowledge to the extent possible
  12. *Leverage current and developing CDS and genomics standards*
  13. Support a CDS knowledge base deployed at and developed by multiple independent organizations
  14. *Access and transmit only the genomic information necessary for CDS*

Murugan M, Babb LJ, Taylor CO et al. Genomic Considerations for FHIR: eMERGE Implementation Lessons. BioRxiv. 2021. https://www.biorxiv.org/content/10.1101/2021.01.31.429037v1.full

Considerations for revising technical desiderata

- Monthly eMERGE EHRI virtual workgroup meetings
  - Framework to classify and synthesize gCDS implementation
  - Documented current state at final eMERGE III in-person meeting (Feb 2020)

- Results from brainstorming potential hazards related to gCDS implementation
  - eMERGE in-person meeting June 21, 2019 in Seattle, WA
  - 25 potential hazards, 4 themes

Areas of focus in eMERGE III EHRI Working group: alert-based gCDS

- Pharmacogenomics alert on drug orders
- New variant knowledge updates to previous results

Table 1
Potential examples of CDS leveraging WGS data.

CDS type	Clinical genomics example
Medication dosing support	CDS automatically adjusts warfarin dosing as a result of known alleles in the VKORC1 and CYP2C9 genes
Order facilitators	An order for colonoscopy is recommended at a younger age as a result of known pathogenic mutations in genes associated with colon cancer
Alerts and reminders	During medication ordering, gene variants known to affect drug pharmacokinetics are checked and clinicians are alerted to potential gene-drug interactions
Relevant information display	Context aware infobuttons in the problem list leverage genome data to provide genetic risk information for a patient with breast cancer
Expert systems	The EHR provides a 10-year cardiovascular disease risk score based on clinical, environmental, and genetic risk factors
Workflow support	The EHR schedules a genetic counseling consultation during prenatal visit due to presence of an X-linked disease gene variant

Welch B, Eilbeck K, Del Fiol G, et al. Technical desiderata for the integration of genomic data with clinical decision support. J Biomed Inform. 2014 Oct;51:3-7. doi: 10.1016/j.jbi.2014.05.014

Areas of focus for eMERGE III EHRI Working group: gCDS architecture

- Ancillary Genomic System

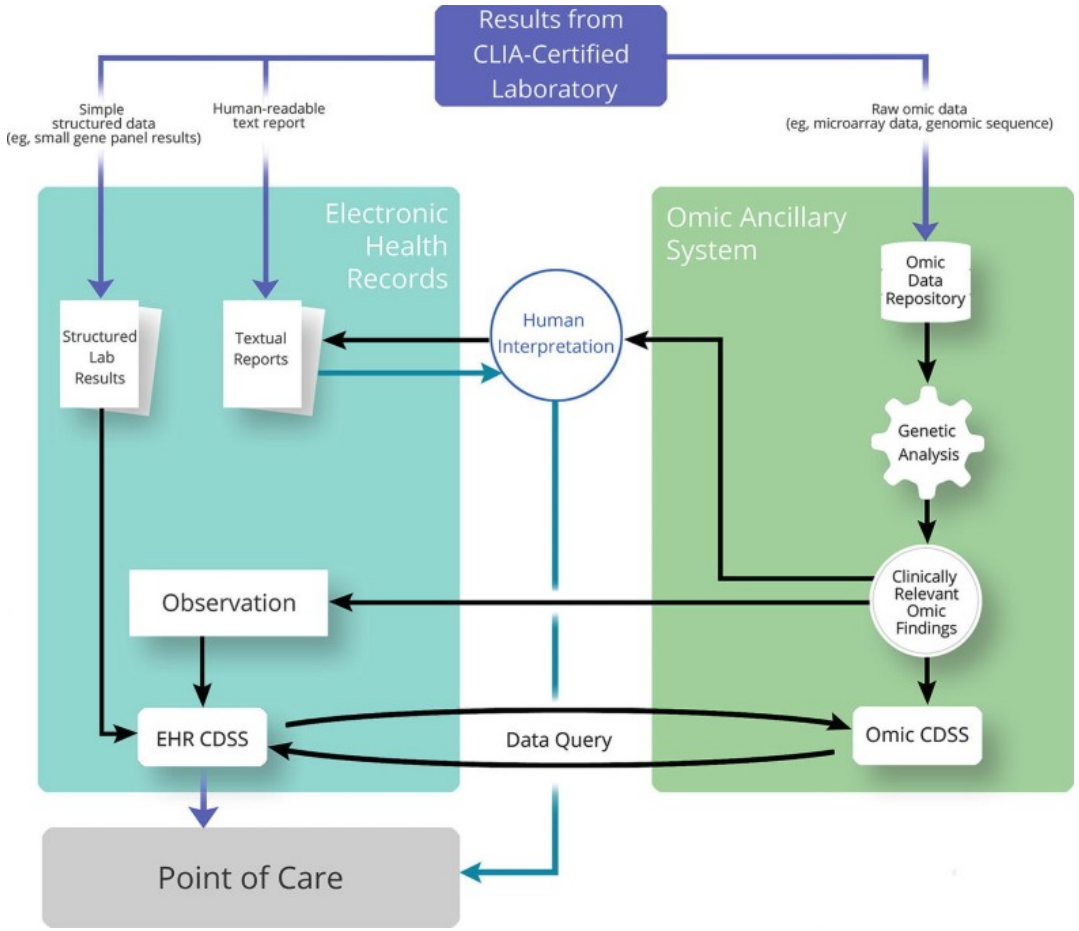
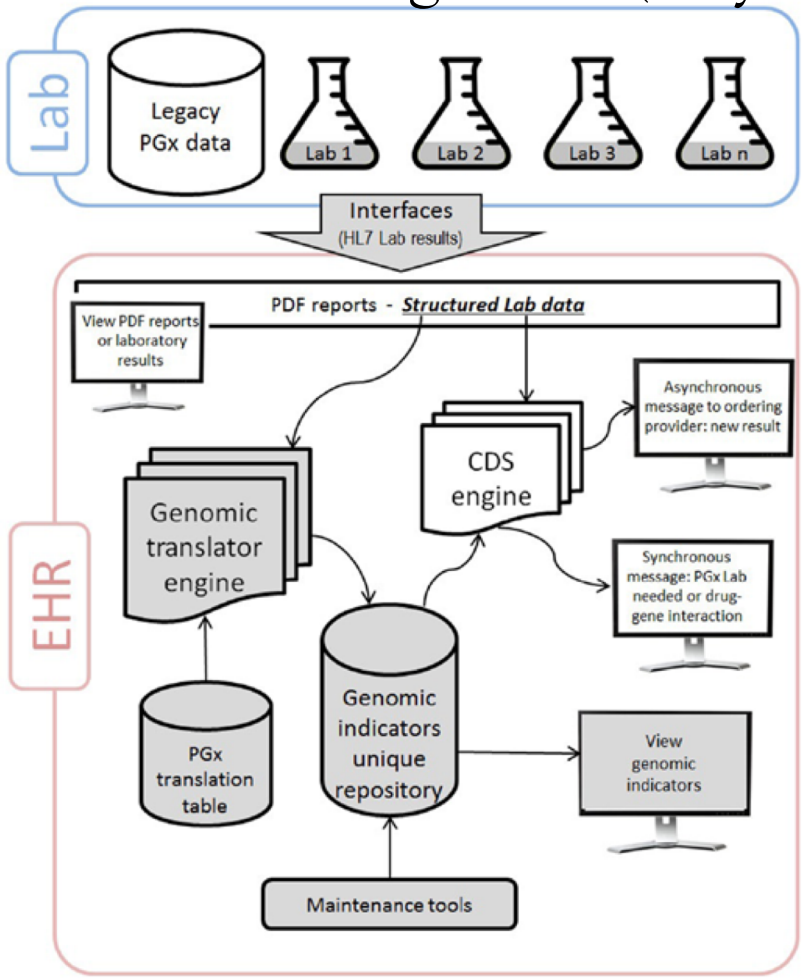


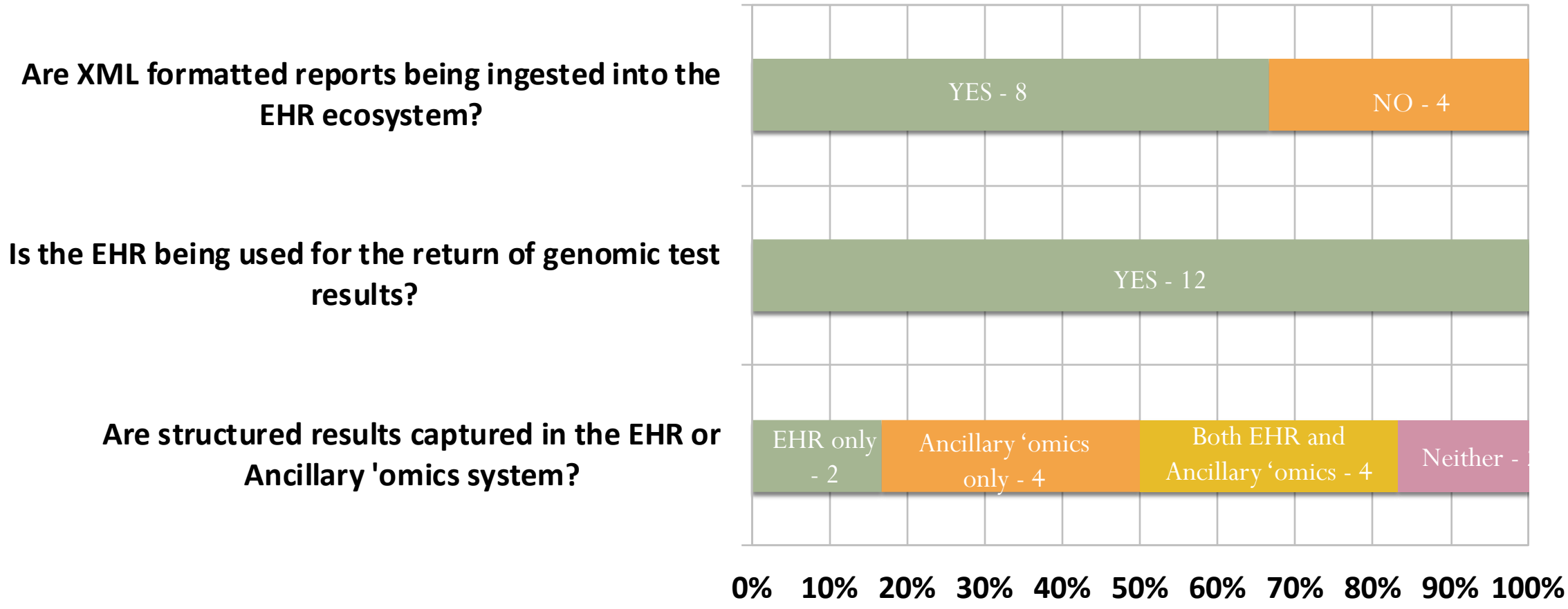
Fig. 17.3 from Rasmussen LV, et al. The Genomic Medical Record and Omic Ancillary Systems. Personalized and Precision Medicine Informatics. Springer, Cham, 2020. 253-275. (based on Starren et al., JAMA 2013)

- EHR Centered Management (Mayo example)



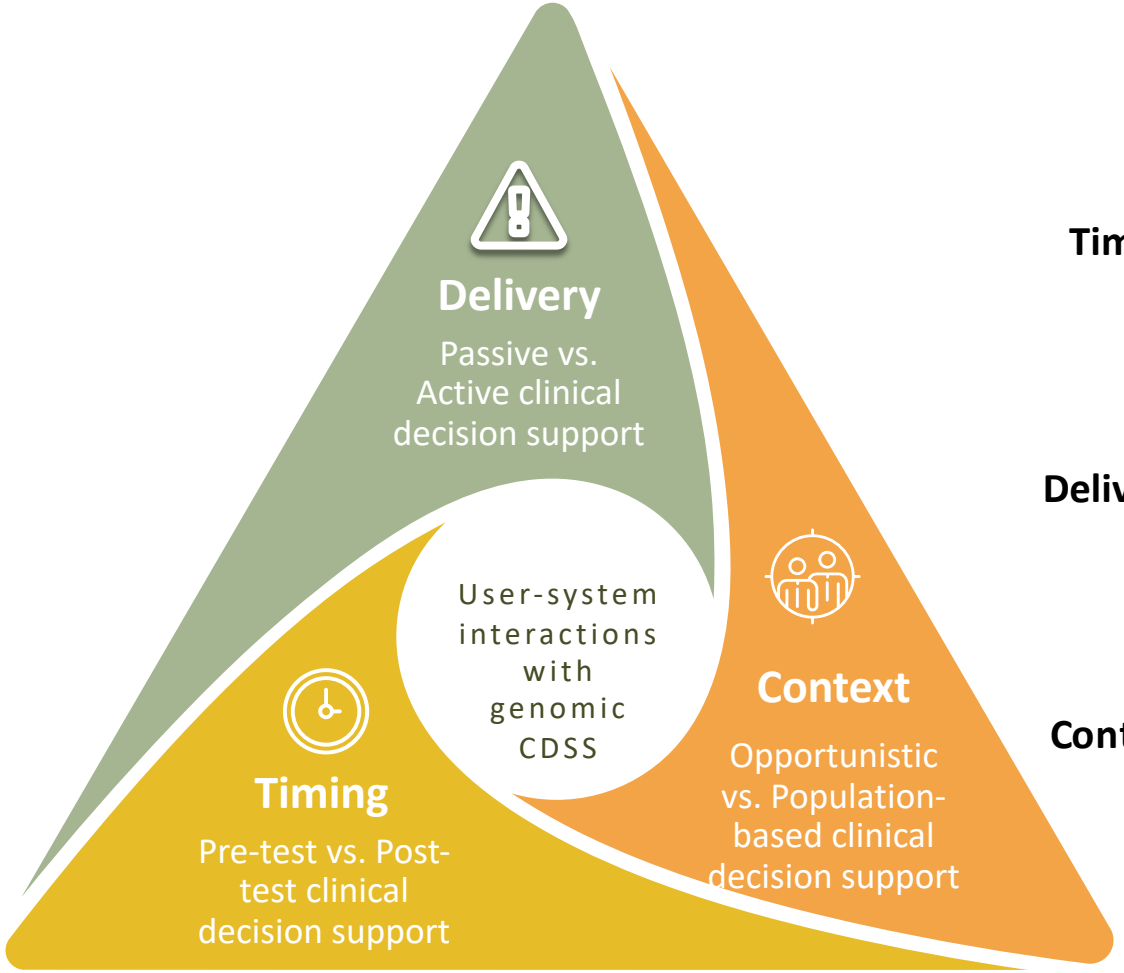
Caraballo PJ, Sutton JA, Giri J, et al. Integrating pharmacogenomics into the electronic health record by implementing genomic indicators. JAMIA. 2020 Jan;27(1):154-158. https://doi-org.proxy1.library.jhu.edu/10.1093/jamia/ocz177

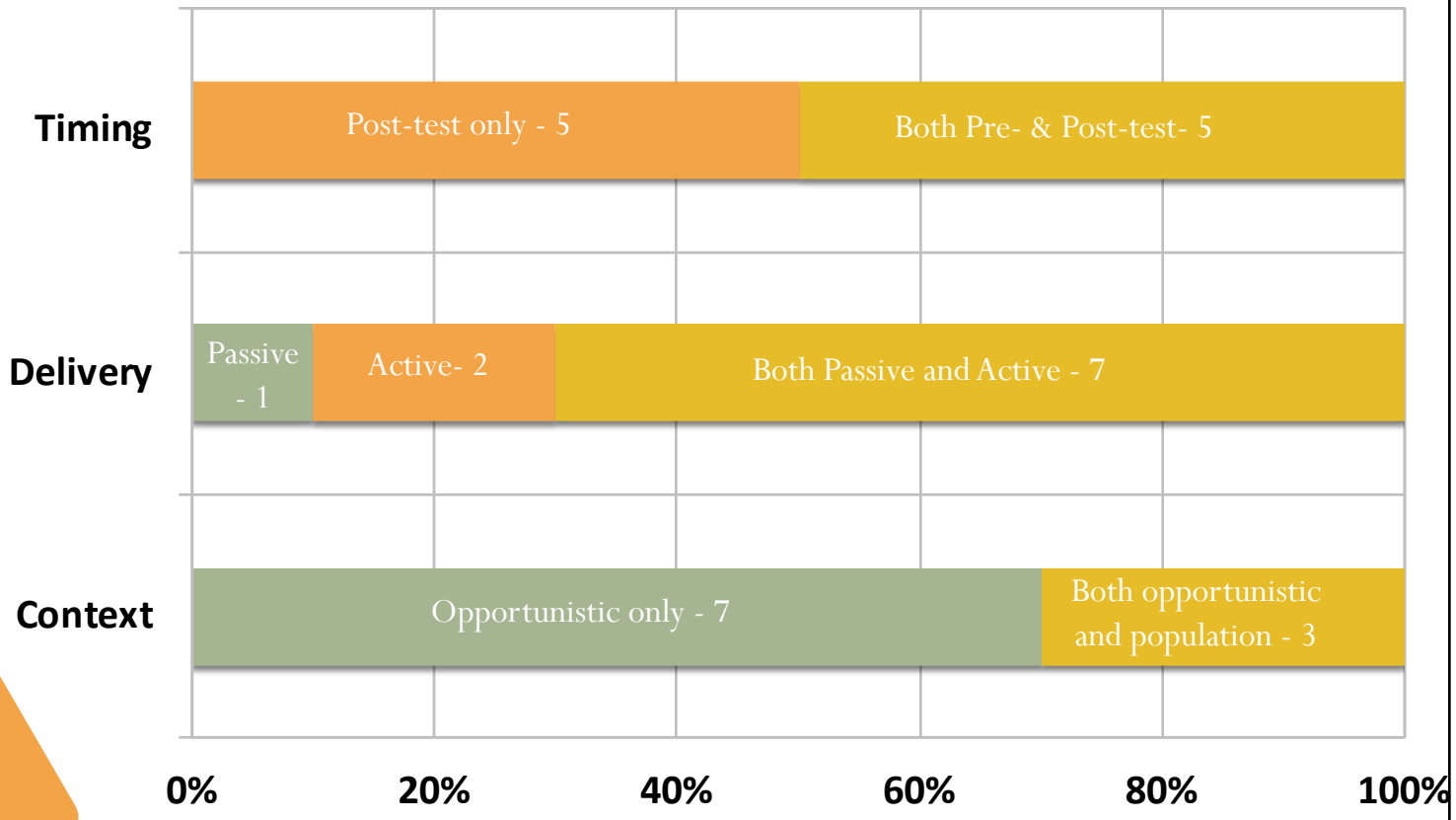
gCDS architecture use among eMERGE III institutions



Taylor CO, Rasmussen LV, Rasmussen-Torvik LJ, et al.Facilitating Genetics Aware Clinical Decision Support: Putting the eMERGE Infrastructure into Practice. ACI Open. (accepted)

gCDS implementation characteristics among eMERGE III institutions





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Considerations for revising technical desiderata

- Monthly eMERGE EHRI virtual workgroup meetings
  - Framework to classify and synthesize gCDS implementation
  - Documented current state at final eMERGE III in-person meeting (Feb 2020)

Series of articles in ACI Open describing lessons learned

Considerations for revising technical desiderata

Solution
Encount
Genomi

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ACI Open 2020;4:e132–e135.

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THIEME OPEN ACCESS

Pilot Implementation of Clinical Genomic Data into the Native Electronic Health Record:

THIEME OPEN ACCESS

Deploying Clinical Decision Support for Familial Hypercholesterolemia

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Results from brainstorming potential hazards related to gCDS implementation in eMERGE EHRI Working group

- Inappropriate alert firing context
  - Alert goes to wrong clinician(s)
  - Alert does not reach all affected family members
- Technical issues
  - Message lost during transmission between lab and clinic/provider
  - Mismatch between the format of the data/result after an update (important for triggering an alert)
- User experience problems
  - Clinician is alerted and misinterprets the guidance
  - No disclosure of alert to the patient (even though in the record)
- Knowledge maintenance
  - Lab is no longer around to provide updates
  - Discordant lab interpretations are not resolved

Taylor CO, Rasmussen LV, Rasmussen-Torvik LJ, et al.Facilitating Genetics Aware Clinical Decision Support: Putting the eMERGE Infrastructure into Practice. ACI Open. (accepted)

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More in depth hazard analysis exercise needed

Risk Index Table

Probability of Occurrence	Severity I Catastrophic (Death, serious injury)	Severity II Significant (Reversible serious injury)	Severity III Marginal (Inconvenience)	Severity IV Negligible
Frequent	1	3	7	13
Probable	2	5	9	16
Occasional	4	6	11	18
Remote	8	10	14	19
Improbable	12	15	17	20

Risk Index Table

HAZARD RISK INDEX	ACCEPTANCE CRITERIA
1 to 5	Unacceptable
6 to 9	Undesirable: Written and reviewed decision required to proceed
10 to 16	Acceptable upon completion of quality assurance review
17 to 20	Acceptable without review

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Series of articles in ACI Open describing lessons learned -> Content analysis (?)

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Research strategy areas to achieve goals of the desiderata

The international journal of science

nature

Perspective

Strategic vision for improving human health at The Forefront of Genomics

https://doi.org/10.1038/s41586-020-2817-4
Received: 30 June 2020
Accepted: 4 September 2020
Published Online: 28 October 2020
Check for updates

Eric D. Green[1] ✉, Chris Gunter[1], Leslie G. Biesecker[1], Valentina Di Francesco[1], Carla L. Easter[1], Elise A. Feingold[1], Adam L. Felsenfeld[1], David J. Kaufman[1], Elaine A. Ostrander[1], William J. Pavan[1], Adam M. Phillippy[1], Anastasia L. Wise[1], Jyoti Gupta Dayal[1], Britny J. Kish[1], Allison Mandich[1], Christopher R. Wellington[1], Kris A. Wetterstrand[1], Sarah A. Bates[1] Darryl Leja[1], Susan Vasquez[1], William A. Gahl[1], Bettie J. Graham[1], Daniel L. Kastner[1], Paul Liu[1], Laura Lyman Rodriguez[1], Benjamin D. Solomon[1], Vence L. Bonham[1], Lawrence C. Brody[1], Carolyn M. Hutter[1] & Teri A. Manolio[1]

- Genomic data science
  - Effective and efficient management of complex genomic data
  - User-friendly systems for data visualization
  - Risk-stratification and prevention algorithms incorporating common and rare genomic variants from a broad range of population subgroups, and with a range of phenotypic data and environmental information incorporated.
  - Robust validation of algorithms across population subgroups and assessed for effect on patient outcomes and healthcare utilization
- Genomics and society (implementation science)
  - Develop and assess strategies for implementing use of genomic information in clinical care
  - Test approaches for population-wide genomic sequencings

Source: https://www.genome.gov/2020SV

Summary

- eMERGE III architecture as an example
  - Satisfies Masys et al. desiderata to integrate genomic information within the EHR
  - Partially satisfies Welch et al. desiderata to integrate genomic information within CDS capabilities
  - Remaining Welch et al. desiderata satisfied in eMERGE III FHIR pilot
- Considerations for revising technical desiderata
  - Can draw from published lessons learned from gCDS implementations
  - More work is needed to understand potential gCDS infrastructure specific hazards
- Research strategy areas to achieve goals of the desiderata
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References

- Masys DR, Jarvik GP, Abernethy NF, et al. Technical desiderata for the integration of genomic data into Electronic Health Records. J Biomed Inform. 2012 Jun;45(3):419-22. doi: 10.1016/j.jbi.2011.12.005
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Issue 02 · Volume 04 · July 2020

https://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00034447

Acknowledgments

- eMERGE Phase III Network
  - Sandy Aronson, co-Chair, eMERGE Phase III Network EHRI Working Group (Partners Healthcare)
  - Mullai Murugan (Baylor College of Medicine)
  - Larry Babb (Sunquest)
  - Luke Rasmussen, M.S. (Northwestern)
  - Robert R. Freimuth, Ph.D. (Mayo)
  - Ken Wiley, Ph.D. (NHGRI Program Manager)
  - EHRI Working Group members

eMERGE Phase III Network: U01HG008657 (Kaiser Permanente Washington/University of Washington); U01HG008685 (Brigham and Women's Hospital); U01HG008672 (Vanderbilt University Medical Center); U01HG008666 (Cincinnati Children's Hospital Medical Center); U01HG006379 (Mayo Clinic); U01HG008679 (Geisinger Clinic); U01HG008680 (Columbia University Health Sciences); U01HG008684 (Children's Hospital of Philadelphia); U01HG008673 (Northwestern University); U01HG008701 (Vanderbilt University Medical Center serving as the Coordinating Center); U01HG008676 (Partners Healthcare/Broad Institute); U01HG008664 (Baylor College of Medicine); and U54MD007593 (Meharry Medical College).

Thank you

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