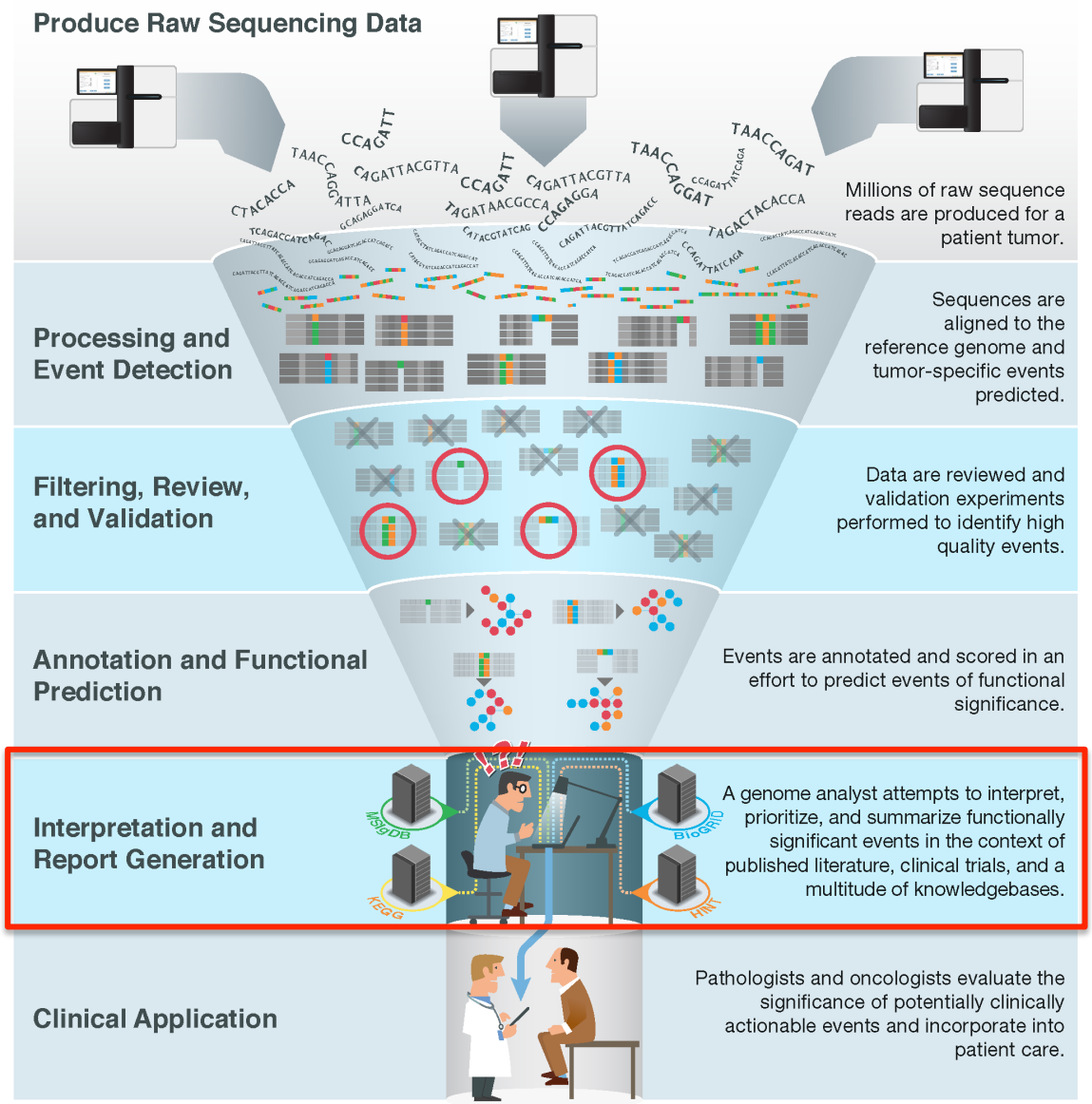
Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

Variant Interpretation for Cancer Consortium (VICC)

www.cancervariants.org

Problem: clinical interpretation of genomic alterations remains a major bottleneck for realizing precision medicine



Good BM, Ainscough BJ, McMichael JF, Su AI†, Griffith OL†. 2014. Genome Biology. 15(8):438.

Clinical interpretations of variants are currently created in academic silos or in restricted-access commercial settings

Genomic Alterations

Gene Alteration	Interpretation
PIK3CA H1047R	Mutations in PIK3CA have been reported in 26% to 33% of breast cancer cases (COSMIC, Jun 2012 and Kalinsky et al., 2009; 19671852). Activating mutations in PIK3CA, such as the one seen here, may predict sensitivity to inhibitors of PI3 kinase or its downstream signaling pathway (the PI3K/Akt/mTOR pathway) (Huang et al., 2007; 18079394). The mTOR inhibitors temsirolimus and everolimus have been tested in several clinical trials in breast cancer, and have been approved by the FDA for use in other tumor types. Inhibitors of PI3K and Akt are currently in clinical trials in breast cancer, alone or in combination with other therapies. PIK3CA mutations may play a role in resistance to hormonal therapy in ER+ breast cancers (Miller et al., 2011; 22114931). Activating mutations in PIK3CA may also confer resistance to anti-Her2 therapies (Chakrabarty et al., 2010; 20581867, Kataoka et al., 2010; 19633047, Wang et al., 2011; 21676217); combined inhibition of Her2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation, though this remains an area of active investigation.
CCND1 amplification	CCND1 amplification has been reported in approximately 10-15% of invasive breast cancers, more frequently in BRCA-negative cancers (Elsheikh et al., 2008; 17653856, Bane et al., 2011; 21327470). There are no approved therapies that directly target the protein product of CCND1 (Cyclin D1); however, CCND1 amplification may predict sensitivity to inhibitors of Cdk4 and Cdk6, which are currently under investigation in clinical trials. Overexpression of Cyclin D1 has also been associated with resistance to endocrine therapy in breast cancer (reviewed in Lange et al., 2011; 21613412; Musgrove and Sutherland, 2009; 19701242, Butt et al., 2005; 16113099).
CDH1 E167*	CDH1 mutations are present in approximately 17% of breast cancers, and more often in luminal type cancers (COSMIC, Jun 2012, Hollestelle et al., 2010; 19593635). Loss of the E-cadherin protein, which is encoded by the CDH1 gene, has been associated with poor prognosis in triple negative breast cancer (Kashiwagi et al., 2010; 20551954, Tang et al., 2011; 21519872). Presently, there are no targeted therapies to address loss of CDH1/E-cadherin.

A coordinated public effort is needed to create and maintain comprehensive interpretations of clinical actionability

Multiple groups are now curating clinical interpretations for cancer variants – Problem too big for any one group…

- **CIViC (WashU)**
- **Cancer Genome Interpreter (Barcelona)**
- **OncoKB (MSKCC)**
- **PMKB (Cornell)**
- **JAX-Clinical Knowledgebase (Jackson lab)**
- **MolecularMatch**
- MyCancerGenome (Vanderbilt)
- KnowledgeBase for Precision Oncology (MD Anderson)
- CanDL (Ohio State)
- COSMIC (Sanger)
- Gene Drug Knowledge Database
- PharmGKB
- ClinVar/ClinGen

- Many ad hoc “databases” at academic centers and hospitals
- Industry (Illumina, Agilent, HLI, etc)

The problem in a nutshell – Representative interpretations from 3 knowledgebases use a variety of custom nomenclature, ontologies, etc

OncoKB

Gene: BRAF (Entrez: 673)
Isoform: ENST00000288602 RefSeq: NM_004333.4
Variant: V600E (????)
Disease: Melanoma (oncotree)
Drug: Dabrafenib
knownEffect: Sensitive
Level: 2B
ApprovedIndications: Dabrafenib is FDA-approved for BRAF V600E mutant unresectable or metastatic melanoma.

CIViC
Clinical Interpretations of Variants in Cancer

Gene: BRAF (Entrez: 673)
Isoform: ENST00000288602.6
Variant: V600E (chr7:g.140453136A>T)
Disease: Skin Melanoma (DOID:8923)
Drug: Dabrafenib + Trametinib
Clinical Significance: Sensitivity
Level: A – Validated
Evidence statement: Open-label, randomized phase 3 trial with 704 patients with metastatic melanoma with a BRAF V600 mutation. Patients were randomized ...

PMKB

Gene: BRAF (???)
Isoform: ENST00000288602
Variant: V600E (7:140453136-140453136)
Tumor: Melanom; Tissue: Skin
Drug: ???
Clinical Significance: ???
Tier: 1
Evidence statement: ... Various B-Raf inhibitors(Vemurafenib, Dabrafenib) have been FDA approved for melanoma therapy in certain settings.

Variant Interpretation for Cancer Consortium (VICC) formed to address this problem

Global Alliance for Genomics & Health

- Year Started: 2016 (AACR GA4GH meeting)
- Country: Global – USA, Barcelona, UK
- Institution(s): WashU, MSKCC, DFCI, OHSU, IRB, Cornell, MolecularMatch, …
- Mission:
  - Global integration of knowledgebases for clinical interpretation of cancer variants
- Major milestones
  - Eight knowledgebases have committed to participate
  - Six knowledgebases have been integrated
  - Alpha query interface now live
- Clinical Focus
  - Ultimate goal – expert curated interpretations integrated into clinical reports

Guiding Principles

- Commit to min. set of elements for sharing variant interpretations
- Focus on published findings to avoid linking variants to individuals
- Release content under permissive license (e.g., CC0)
- Released software in public repositories with open source licenses. (i.e., GitHub/MIT)
- Provide documented public APIs
- Allow bulk downloads
- Use GA4GH standards

http://cancervariants.org/principles/

Normalized Evidence to AMP Guidelines

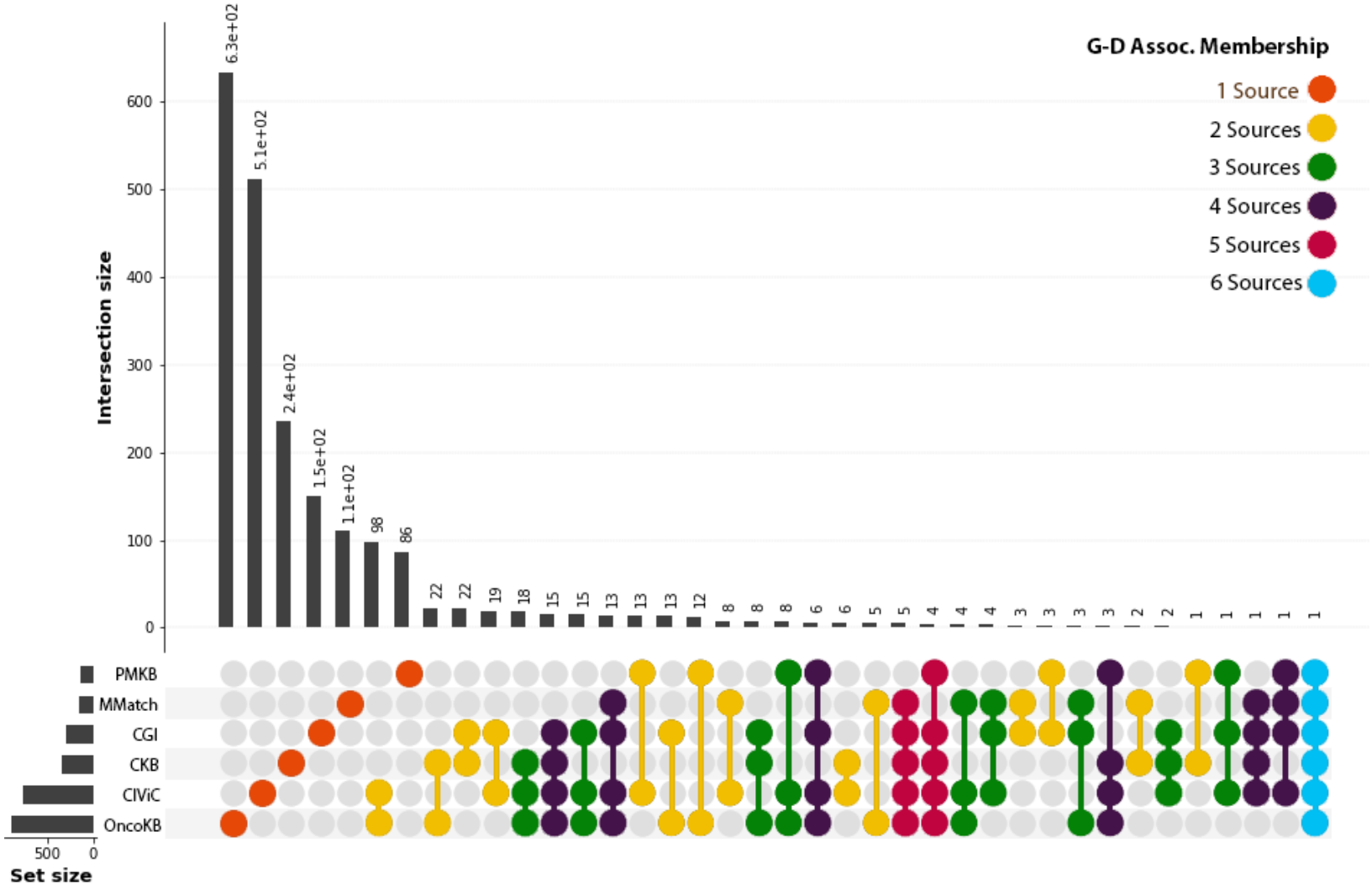
Merged Evidence Levels						
AMP/ASCO/CAP	**Defining Characteristics**	**CIViC (Pd, Pg, Dg, Pdsp)**	**OncoKB (Pd)**	**CKB (Pd, Pg, Dg, Pdsp)**	**CGI (Pd)**	**PMKB (Pd, Pg, Dg, Pdsp)**
Level A	*Evidence from professional guidelines or FDA-approved therapies relating to a biomarker and disease.*	Level A	Level 1 / R1	Guideline / FDA Approved	Clinical Practice	Tier 1
Level B	*Evidence from clinical trials or other well-powered studies in clinical populations, with expert consensus.*	Level B 4/5-star	Level 2A	Phase III	Clinical Trials III-IV	
Level C	*Evidence for therapeutic predictive markers from case studies, or other biomarkers from several small studies. Also evidence for biomarker therapeutic predictions for established drugs for different indications.*	Predictive Level C	Level 2B, Level 3	Clinical Study/ Phase I / Phase II	Clinical Trials I-II, Case Reports	Tier 2
Level D	*Preclinical findings or case studies of prognostic or diagnostic biomarkers. Also includes indirect findings.*	Non-predictive Level C / Lev	Level 4	Phase 0, Pre-clinical	Pre-clinical Data	Tier 3
* These rankings are not available to the public						

Li et al. J Mol Diagn. 2017 Jan;19(1):4-23.

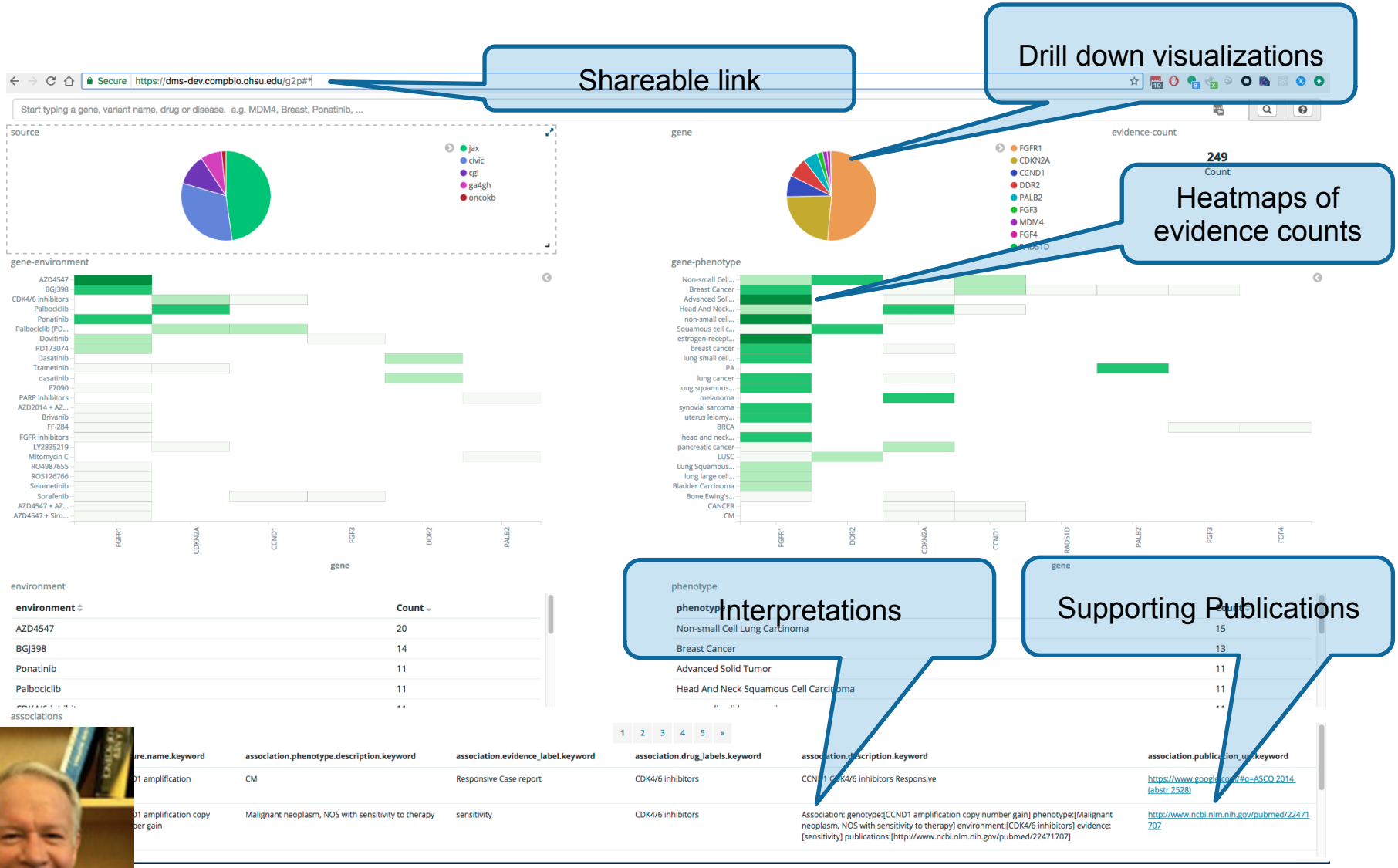
Over 17,000 associations integrated to date from six major knowledgebases

Resource	Associations
Knowledgebase for Clinical Interpretations of Variants in Cancer (CIViC)	2713
Cancer Genome Interpreter (CGI)	1429
Clinical Knowledgebase (CKB)	6513
Precision Oncology Knowledge Base (OncoKB)	4125
Precision Medicine Knowledgebase (PMKB)	606
MolecularMatch	2083

Most associations unique to one resource. Large problem space + more normalization work



Alpha site now live for cross-knowledgebase queries

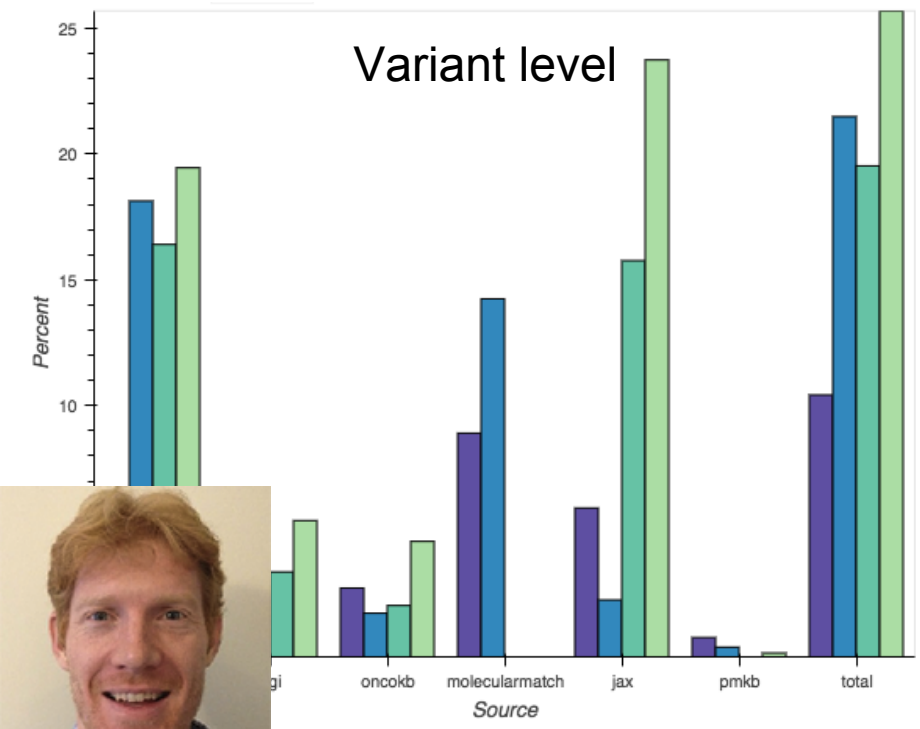


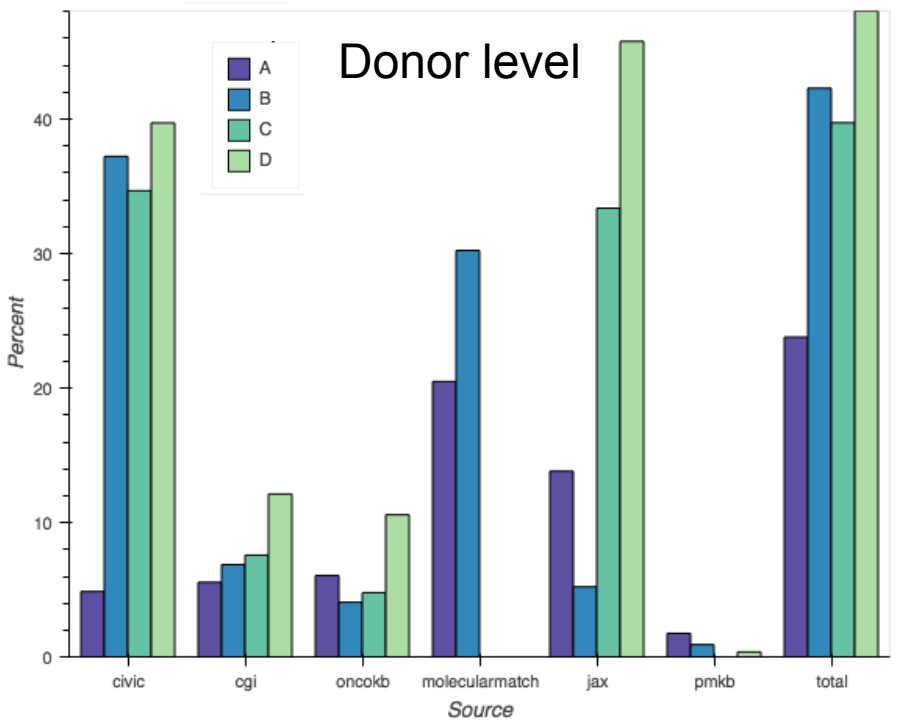
https://g2p-ohsu.ddns.net/

Brian Walsh

Application of VICC data to GENIE

- 28% of non-unique variants represented (1-25% for individual resources)
- 42% of donors have 1+ actionable variant





Synergies with GA4GH Technical Work Streams

Global Alliance for Genomics & Health

Work Stream	Potential Engagement
Discovery / Large-Scale Genomics	Integrate variant interpretations with large-scale genomics efforts
Genomic Knowledge Standards	Variant modeling (equivalence) and exchange. Standards for variant interpretation.
Clinical & Phenotypic Data Capture	Phenotype (disease) modeling, ontologies, and EMR integration
Data Security, Regulatory & Ethics	Patient privacy variant-level data, responsible use (liability) of variant interpretations in clinical contexts

Variant Interpretation Collaboration (VIC) leadership: Seeking participants/contributors

Leadership

Variant Interpretation for Cancer Consortium (VICC)


Obi Griffith
WashU


Malachi Griffith
WashU


Nuria Lopez-Bigas
IRB


David Tamborero
IRB

G2P


Adam Margolin
OHSU

Key Knowledgebase Partners


Nikolaus Schultz
MSKCC


Debyani Chakravarty
MSKCCC


Olivier Elemento
Weill Cornell


Ethan Cerami
DFCI


Catherine Del Vecchio Fitz
DFCI

Knowledgebase Integration


Alex Wagner
WashU


Brian Walsh
OHSU


Jeremy Goecks
OHSU


Georgia Mayfield
OHSU

Virtual Tumor Board

Coming soon ... Seeking key partners

Consortium Participants (Past and Present)

Adam Margolin, Aitana Lebrand, Alberto Cambrosio, Alex Wagner, Alexander Senf, Alexander Wait Zaranek, Anas Belouali, Andra Waagmeester, Andrew Biankin, Andrew Su, Andrey Zapariy, Andy Yates, Bailey Glen, Ben Ainscough, Beth Pitel, Bin Tean The, Brad Chapman, Brian Walsh, Catherine Del Vecchio Fitz, Chris Corless, Chris Sander, Christine Micheel, Chunlei Wu, Daniel Durkin, Daniel Stekhoven, David Chang, David Haussler, David Heckerman, David Masica, David Tamborero, Deborah Ritter, Debyani Chakravarty, Dmitriy Sonkin, Eli Van Allen, Erin Ramos, Ethan Cerami, Etienne Vignola-Gagné, Fiona Cunningham, Gabe Rudy, Georgia Mayfield, Gordana Raca, Greg Stupp, Heidi Sofia, Jacques Beckmann, Jeffrey Rosenfeld, Jeremy Goecks, Jianjiong Gao, Joachim Weischenfeldt, Jonah Campbell, Jonathan Ellis, Jordi Deu, Julia Wilson, Justina Chung, Kevin Osborn, Kiannin Krysiak, Koh Liang Kai, Larry Babb, Lena Dolman, Lillian Siu, Lynn Brazil, Lynn Schriml, Malachi Griffith, Mamatha Shekar, Mark Jensen, Mark Lawler, Maximilian Haeussler, Melanie Courtot, Melissa Haendel, Melissa Landrum, Michael Baudis, Michael Bouziner, Moritz Gerstung, Nikolaus Schultz, Nora Christina Toussaint, Nuria Lopez-Bigas, Obi Griffith, Oliver Hofmann, Olivier Elemento, Paul Leo, Peter Keating, Rachel Liao, Ravi Pandya, Rob Currie, Robert Freimuth, Rodrigo Dienstmann, Sameek Roychowdhury, Sara Gosline, Sara Patterson, Sarah Hunt, Shirley Li, Shruti Rao, Steven Brenner, Subha Madhavan, Susan Mockus, Tero Aittokallio, Trish Whetzel, Ugur Sezerman, William Glen.

http://cancervariants.org/members/

Variant Interpretation Collaboration (VIC) leadership: Seeking participants/contributors

Leadership

Variant Interpretation for Cancer Consortium (VICC)


Obi Griffith
WashU


Malachi Griffith
WashU


Nuria Lopez-Bigas
IRB


David Tamborero
IRB

G2P


Adam Margolin
OHSU

Key Knowledgebase Partners


Nikolaus Schultz
MSKCC


Debyani Chakravarty
MSKCCC


Olivier Elemento
Weill Cornell


Ethan Cerami
DFCI


Catherine Del Vecchio Fitz
DFCI

Knowledgebase Integration


Alex Wagner
WashU


Brian Walsh
OHSU


Jeremy Goecks
OHSU


Georgia Mayfield
OHSU

Virtual Tumor Board

Coming soon ... Seeking key partners

Consortium Participants (Past and Present)

Adam Margolin, Aitana Lebrand, Alberto Cambrosio, Alex Wagner, Alexander Senf, Alexander Wait Zaranek, Anas Belouali, Andra Waagmeester, Andrew Biankin, Andrew Su, Andrey Zapariy, Andy Yates, Bailey Glen, Ben Ainscough, Beth Pitel, Bin Tean The, Brad Chapman, Brian Walsh, Catherine Del Vecchio Fitz, Chris Corless, Chris Sander, Christine Micheel, Chunlei Wu, Daniel Durkin, Daniel Stekhoven, David Chang, David Haussler, David Heckerman, David Masica, David Tamborero, Deborah Ritter, Debyani Chakravarty, Dmitriy Sonkin, Eli Van Allen, Erin Ramos, Ethan Cerami, Etienne Vignola-Gagné, Fiona Cunningham, Gabe Rudy, Georgia Mayfield, Gordana Raca, Greg Stupp, Heidi Sofia, Jacques Beckmann, Jeffrey Rosenfeld, Jeremy Goecks, Jianjiong Gao, Joachim Weischenfeldt, Jonah Campbell, Jonathan Ellis, Jordi Deu, Julia Wilson, Justina Chung, Kevin Osborn, Kiannin Krysiak, Koh Liang Kai, Larry Babb, Lena Dolman, Lillian Siu, Lynn Brazil, Lynn Schriml, Malachi Griffith, Mamatha Shekar, Mark Jensen, Mark Lawler, Maximilian Haeussler, Melanie Courtot, Melissa Haendel, Melissa Landrum, Michael Baudis, Michael Bouziner, Moritz Gerstung, Nikolaus Schultz, Nora Christina Toussaint, Nuria Lopez-Bigas, Obi Griffith, Oliver Hofmann, Olivier Elemento, Paul Leo, Peter Keating, Rachel Liao, Ravi Pandya, Rob Currie, Robert Freimuth, Rodrigo Dienstmann, Sameek Roychowdhury, Sara Gosline, Sara Patterson, Sarah Hunt, Shirley Li, Shruti Rao, Steven Brenner, Subha Madhavan, Susan Mockus, Tero Aittokallio, Trish Whetzel, Ugur Sezerman, William Glen.

Questions?

http://cancervariants.org/members/