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

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

### Genomic Alterations

<table>
<thead>
<tr>
<th>Gene Alteration</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td><strong>PIK3CA H1047R</strong></td>
<td>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.</td>
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<tr>
<td><strong>CCND1 amplification</strong></td>
<td>CCND1 amplification has been reported in approximately 10-15% of invasive breast cancers, more frequently in BRCA-negative cancers (Elsheikh et al., 2008; 17653858, 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).</td>
</tr>
<tr>
<td><strong>CDH1 E167</strong>*</td>
<td>CDH1 mutations are present in approximately 17% of breast cancers, and more often in luminal type cancers (COSMIC, Jun 2012, Hollesteke 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.</td>
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</tbody>
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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**

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

- 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

<table>
<thead>
<tr>
<th>Merged Evidence Levels</th>
<th>Defining Characteristics</th>
<th>CIViC (Pd, Pg, Dg, Pdsp)</th>
<th>OncoKB (Pd)</th>
<th>CKB (Pd, Pg, Dg, Pdsp)</th>
<th>CGI (Pd)</th>
<th>PMKB (Pd, Pg, Dg, Pdsp)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td>Evidence from professional guidelines or FDA-approved therapies relating to a biomarker and disease.</td>
<td>Level A</td>
<td>Level 1 / R1</td>
<td>Guideline / FDA Approved</td>
<td>Clinical Practice</td>
<td>Tier 1</td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td>Evidence from clinical trials or other well-powered studies in clinical populations, with expert consensus.</td>
<td>Level B 4/5-star</td>
<td>Level 2A</td>
<td>Phase III</td>
<td>Clinical Trials III-IV</td>
<td></td>
</tr>
<tr>
<td><strong>Level C</strong></td>
<td>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.</td>
<td>Predictive Level C</td>
<td>Level 2B, Level 3</td>
<td>Clinical Study/ Phase I / Phase II</td>
<td>Clinical Trials I-II, Case Reports</td>
<td>Tier 2</td>
</tr>
<tr>
<td><strong>Level D</strong></td>
<td>Preclinical findings or case studies of prognostic or diagnostic biomarkers. Also includes indirect findings.</td>
<td>Non-predictive Level C / Level 4</td>
<td>Level 4</td>
<td>Phase 0, Pre-clinical</td>
<td>Pre-clinical Data</td>
<td>Tier 3</td>
</tr>
</tbody>
</table>

* These rankings are not available to the public

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

<table>
<thead>
<tr>
<th>Resource</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledgebase for Clinical Interpretations of Variants in Cancer (CIViC)</td>
<td>2713</td>
</tr>
<tr>
<td>Cancer Genome Interpreter (CGI)</td>
<td>1429</td>
</tr>
<tr>
<td>Clinical Knowledgebase (CKB)</td>
<td>6513</td>
</tr>
<tr>
<td>Precision Oncology Knowledge Base (OncoKB)</td>
<td>4125</td>
</tr>
<tr>
<td>Precision Medicine Knowledgebase (PMKB)</td>
<td>606</td>
</tr>
<tr>
<td>MolecularMatch</td>
<td>2083</td>
</tr>
</tbody>
</table>
Most associations unique to one resource. Large problem space + more normalization work.
Alpha site now live for cross-knowledgebase queries

Shareable link

Drill down visualizations

Heatmaps of evidence counts

Interpretations

Supporting Publications

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

<table>
<thead>
<tr>
<th>Work Stream</th>
<th>Potential Engagement</th>
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<tbody>
<tr>
<td>Discovery / Large-Scale Genomics</td>
<td>Integrate variant interpretations with large-scale genomics efforts</td>
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<tr>
<td>Genomic Knowledge Standards</td>
<td>Variant modeling (equivalence) and exchange. Standards for variant interpretation.</td>
</tr>
<tr>
<td>Clinical &amp; Phenotypic Data Capture</td>
<td>Phenotype (disease) modeling, ontologies, and EMR integration</td>
</tr>
<tr>
<td>Data Security, Regulatory &amp; Ethics</td>
<td>Patient privacy variant-level data, responsible use (liability) of variant interpretations in clinical contexts</td>
</tr>
</tbody>
</table>
Variant Interpretation Collaboration (VIC) leadership: Seeking participants/contributors

http://cancervariants.org/members/
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Questions?

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