GENOMENON®

*POWERING EVIDENCE-BASED GENOMICS*

# Characterizing Targeted Cancer Therapeutics The Comprehensive Gene Fusion Database

Evidence-Based Gene Fusion Landscape

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*Founder and Chief Science Officer, Genomenon*

Molecular Genetic Pathology, University of Michigan

Weintraub International Graduate Student Award

ProQuest Distinguished Dissertation Award

Benjamin Castleman Award

*Outline*

# GENE FUSION DATABASE WITH MASTERMIND

- Background - Fusions
- Gene Fusion Database
  - Summary Data
  - Example Data
  - Use Cases
- Summary
- Questions


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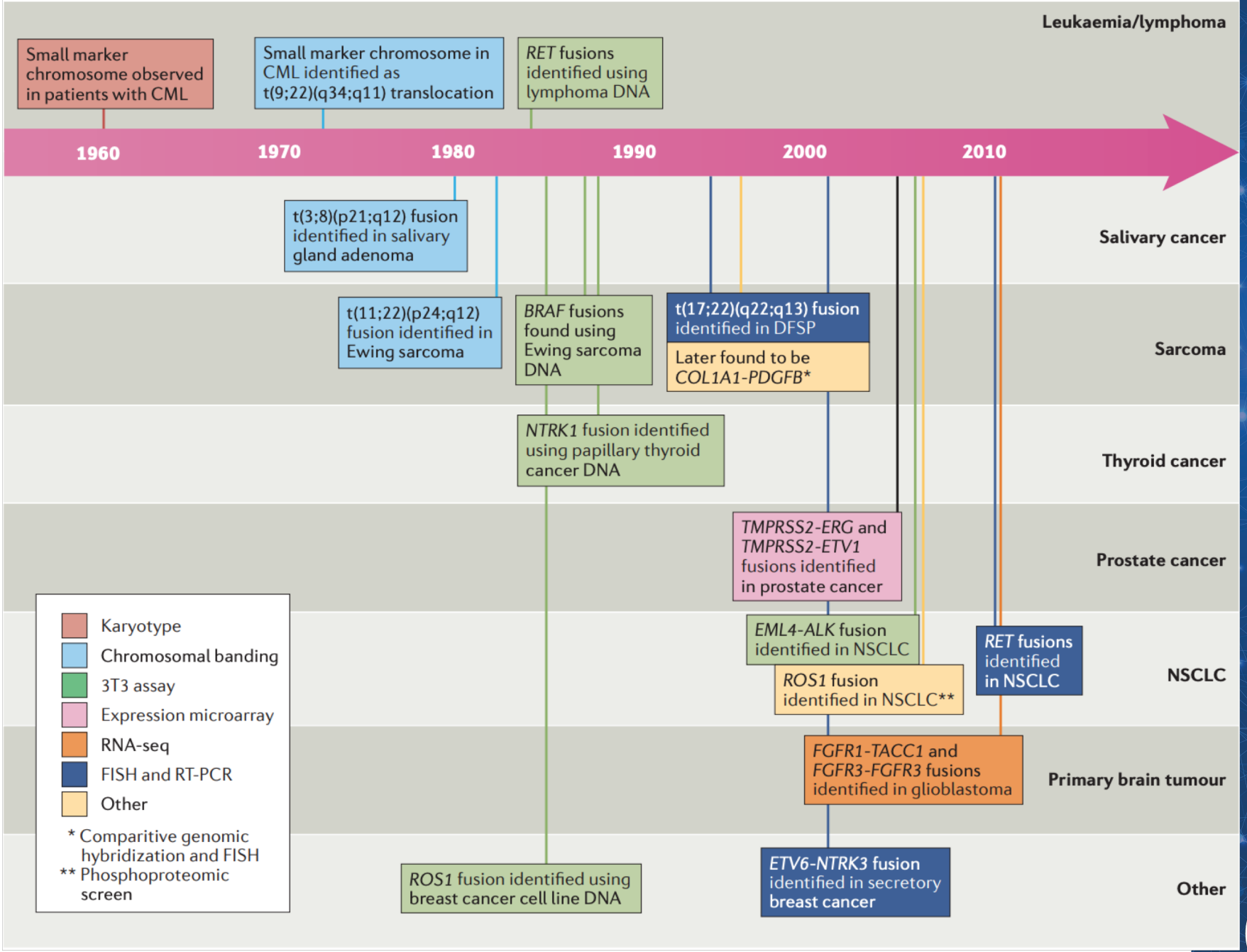
# HISTORY OF GENE FUSIONS IN CANCER






*Fusions in solid tumours: diagnostic strategies, targeted therapy, and acquiring resistance*. Schram et al. 2017 PMID 28857077

# UTILITY OF GENE FUSIONS IN CANCER

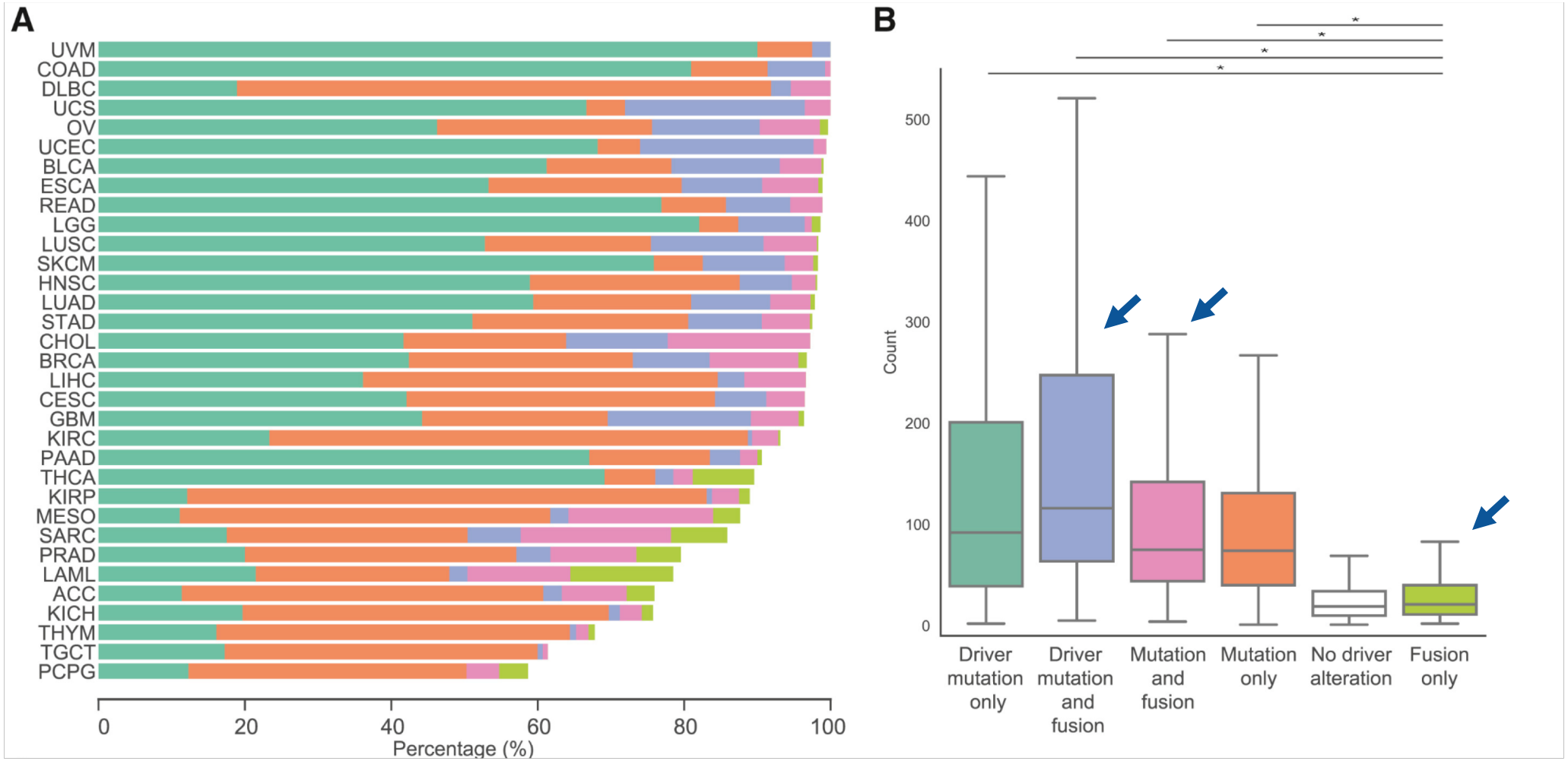
**Box 1. Summary points**

1. Gene fusions are an integral component of the landscape of somatic aberrations in all cancers.
2. Recurrent 5′ fusion genes are generally lineage- and/or cell-type specific.
3. Recurrent 3′ fusion genes in epithelial cancers are usually kinases or transcription factors, similar to the situation in hematological and soft tissue cancers.
4. High-throughput sequencing enables systematic discovery of gene fusions with high sensitivity and precision.
5. High-throughput sequencing often identifies multiple gene fusions in individual samples, presenting a challenge to distinguish oncogenic "driver" from unimportant "passenger" aberrations.
6. Chimeric RNAs expressed independent of chromosomal rearrangements are frequently observed in cancer (and benign) tissues.
7. Functionally recurrent gene fusions provide clinically relevant molecular subclassifications of existing morphological categories of tumors.
8. Functionally recurrent gene fusions that are seen across tissue types define functionally distinct molecular subtypes of cancers.
9. Gene fusions represent personalized therapeutic targets and prognostic and diagnostic markers.



*Landscape of gene fusions in epithelial cancers: seq and ye shall find.* Kumar-Sinha et al. 2015 PMID 26684754

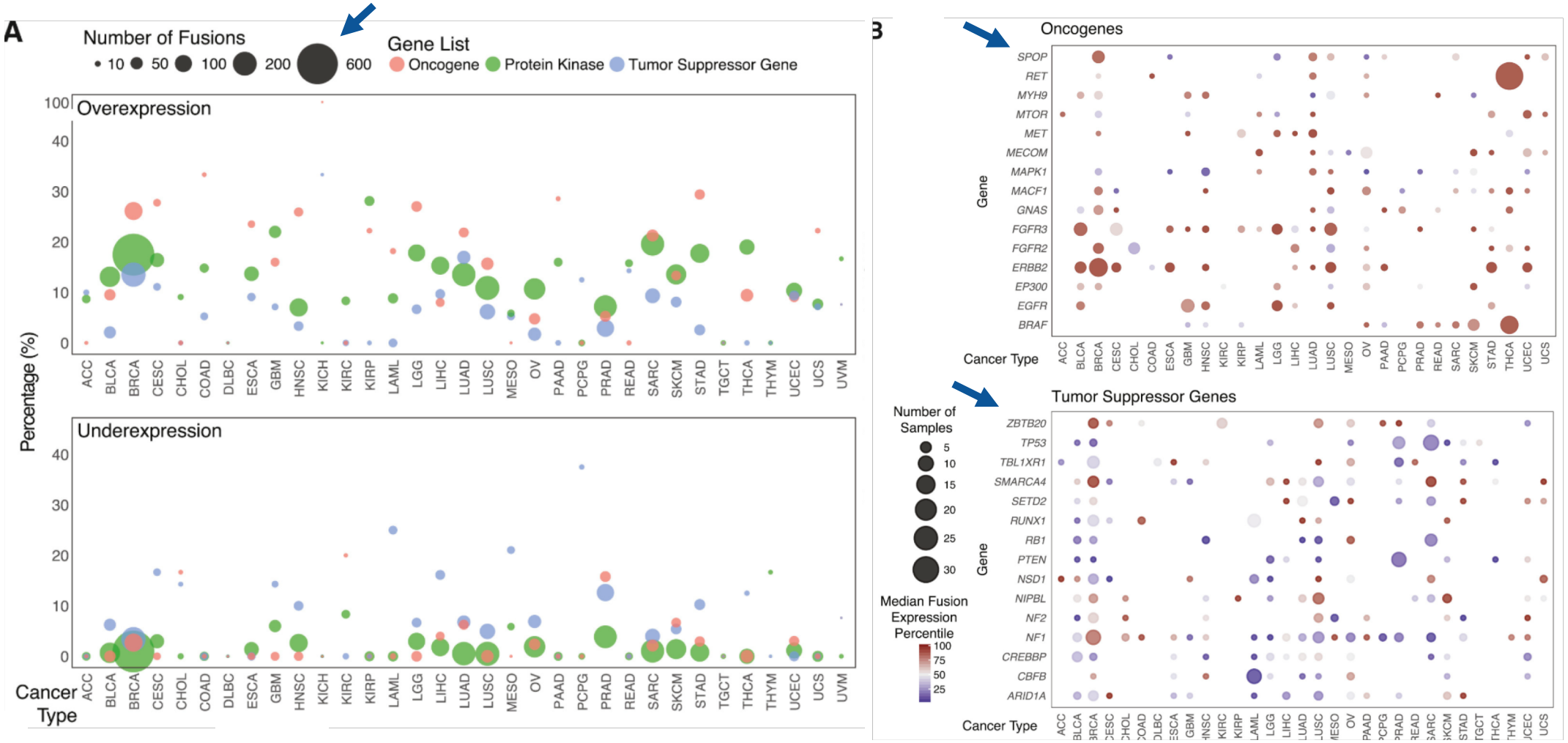
# EXTENT OF GENE FUSIONS IN CANCER






*Driver Fusions and Their Implications in the Development and Treatment of Human Cancers.* Gao et al. 2018. PMID 29617662

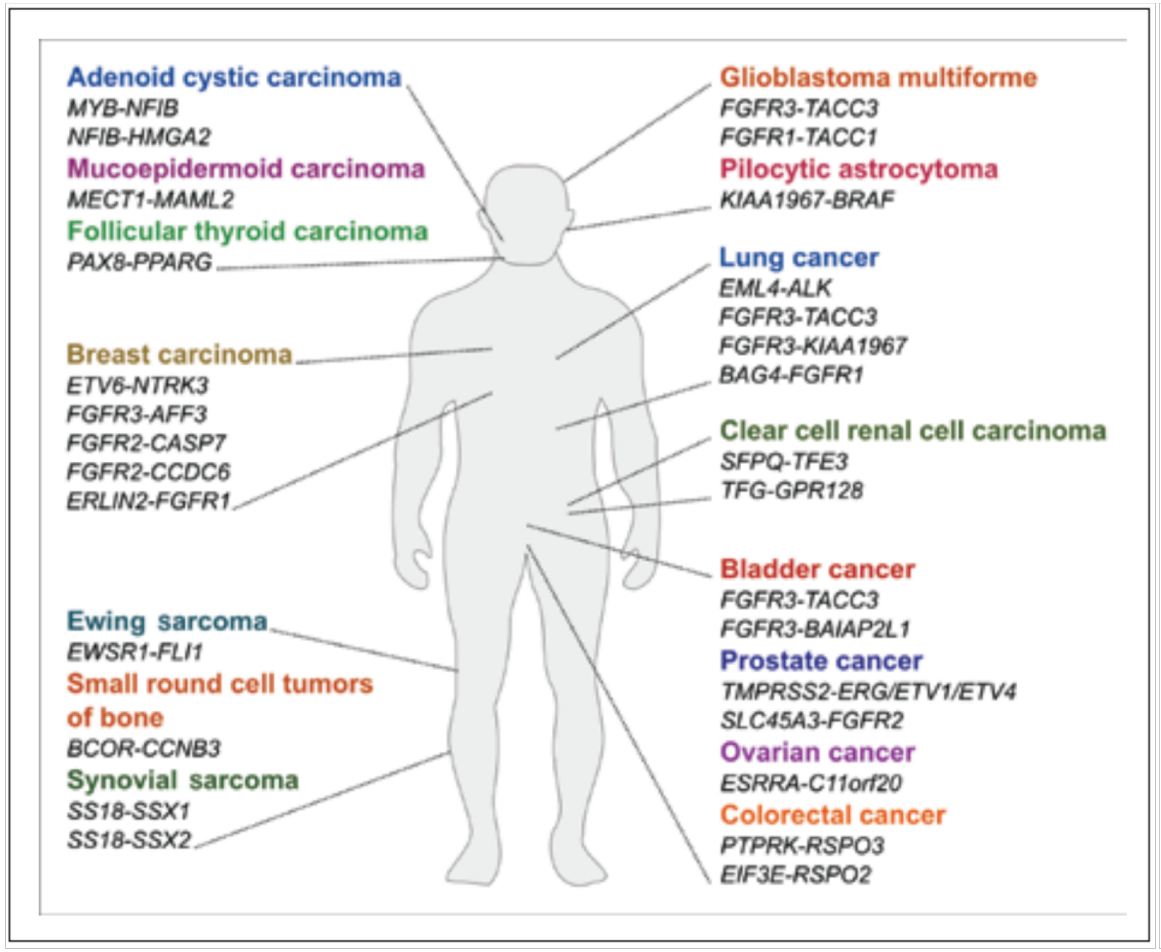
# EXTENT OF GENE FUSIONS IN CANCER






*Driver Fusions and Their Implications in the Development and Treatment of Human Cancers.* Gao et al. 2018. PMID 29617662

# CANCER GENE FUSIONS IN THE CLINIC




| | Alectinib | Apatinib | Brigatinib | Cabozantinib | Ceritinib | Crizotinib | Dabrafenib | Dasatinib | Entrectinib | Erlotinib | Gefitinib | Imatinib | Lapatinib | Larotrectinib | Lorlatinib | Nilotinib | Pazopanib | Ponatinib | Regorafenib | Sorafenib | Sunitinib | Vandetanib | Vemurafenib |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ABL | | | | | | | | X | | | | X | | | | X | | X | | | | | |
| ALK | X | | X | | X | X | | | X | | | | | | X | | | | | | | | |
| AXL | | | | X | | | | | | | | | | | | | | | | | | | |
| BRAF | | | | | | | X | | | | | | | | | | | | X | X | | | X |
| EGFR | | | X | | | | | | | X | X | | X | | | | | | | | | X | |
| FGFR | | | | | | | | | | | | | | | | | | X | X | | | X | |
| FLT3 | | | | X | | | | | | | | | | | | | | X | | X | X | | |
| HER2 | | | | | | | | | | | | | X | | | | | | | | | | |
| KIT | | X | | X | | | | X | | | | X | | | | X | X | X | X | X | X | | |
| MET | | | | X | | X | | | | | | | | | | | | | | | | | |
| PDGFR | | X | | | | | | X | | | | X | | | | X | X | X | X | X | X | | |
| RET | X | X | | X | | | | | | | | | | | | | | X | X | X | X | X | |
| ROS | | | | X | X | X | | | X | | | | | | X | | | | | | | | |
| SRC | | X | | | | | | X | | | | | | | | | | X | | | | X | |
| TIE2 | | | | X | | | | | | | | | | | | | | X | X | | | X | |
| TRK | | | | X | | | | | X | | | | | X | | | | | | | | | |
| VEGFR | | X | | X | | | | | | | | | | | | | X | X | X | X | X | X | |



*Fusion genes in solid tumors: an emerging target for cancer diagnosis and treatment.* Parker et al. 2013. PMID 28857077

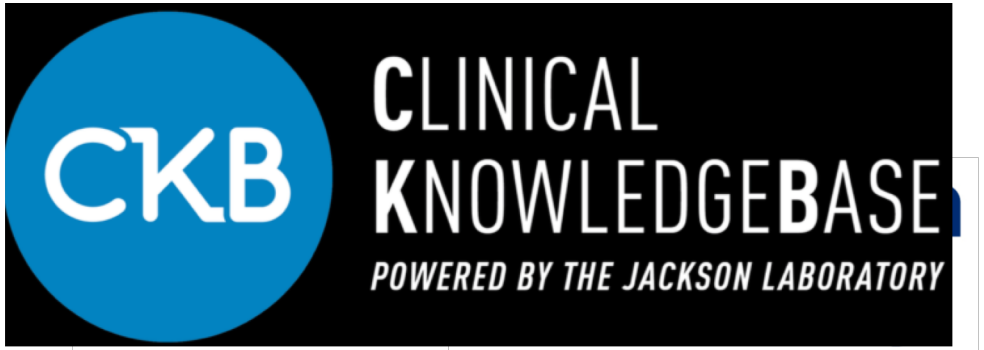
*Fusions in solid tumours: diagnostic strategies, targeted therapy, and acquiring resistance.* Schram et al. 2017 PMID 28857077

# IDENTIFY AND ANNOTATE DISEASE DRIVERS

- Which patient variants are activating & what is the supporting evidence?
- What is the landscape of functional variants for a given gene or pathway?
- Which evidence-based genes should be included on an diagnostic panel?
- Which variants should I include on a disease-specific diagnostic assay?
- Which variants are targetable using precision therapies?

# IDENTIFY AND ANNOTATE DISEASE DRIVERS





*Gene Fusion Database*

# SUMMARY DATA

illumina®
TruSight™ RNA
Fusion Panel

**507**

Total Number of Input Genes

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**1-95**

Fusion Partners per Input Gene

**2,419**

Characterized Gene Fusion Events

**28,688**

Articles Citing Fusion Pairs

*Gene Fusion Database*

# SUMMARY DATA

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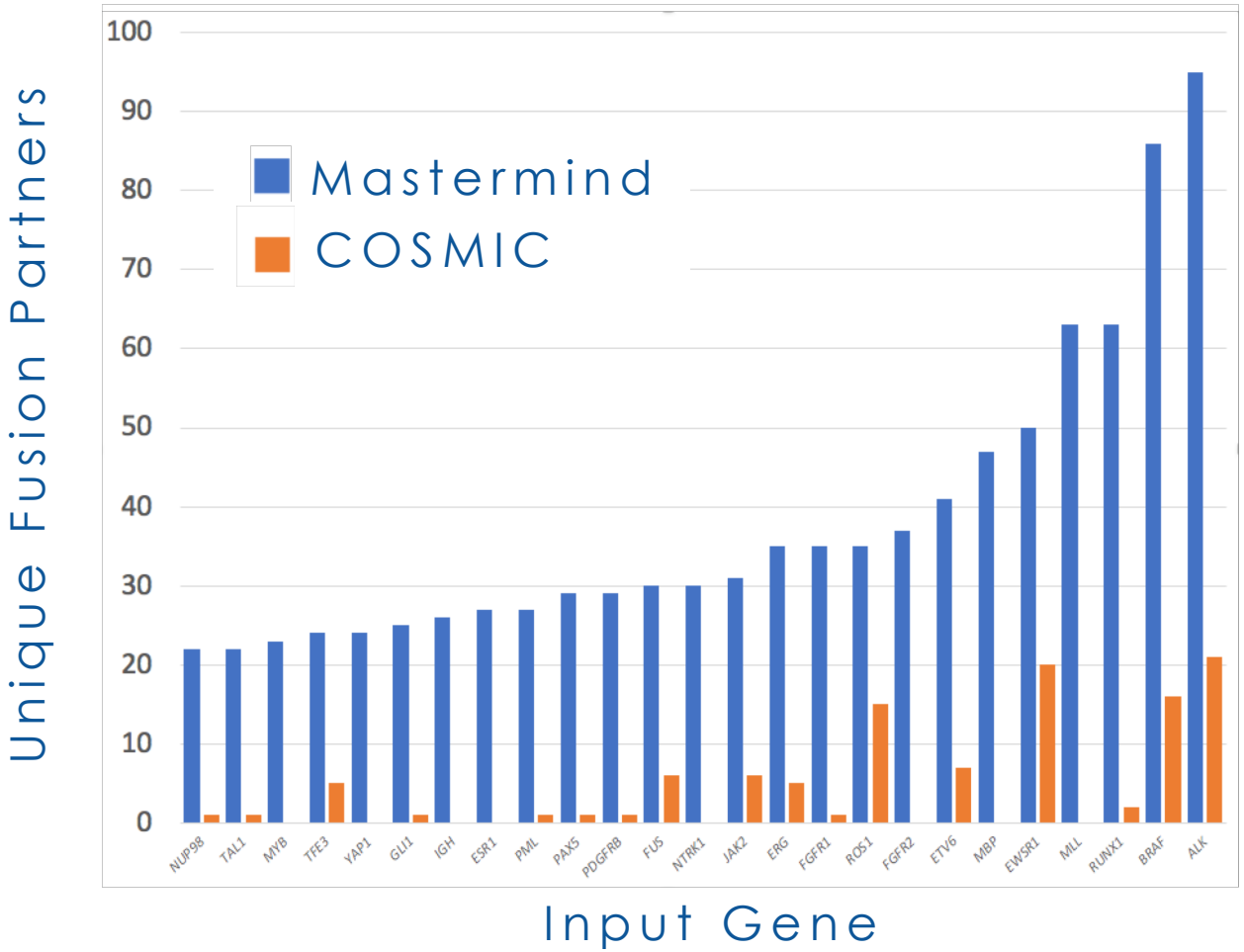
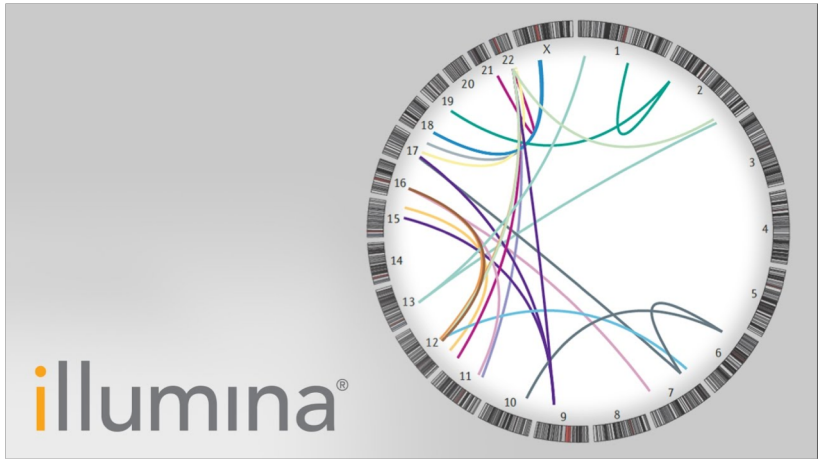


*Genomenon's Approach*

# GENOMIC LANDSCAPING – GENE FUSIONS

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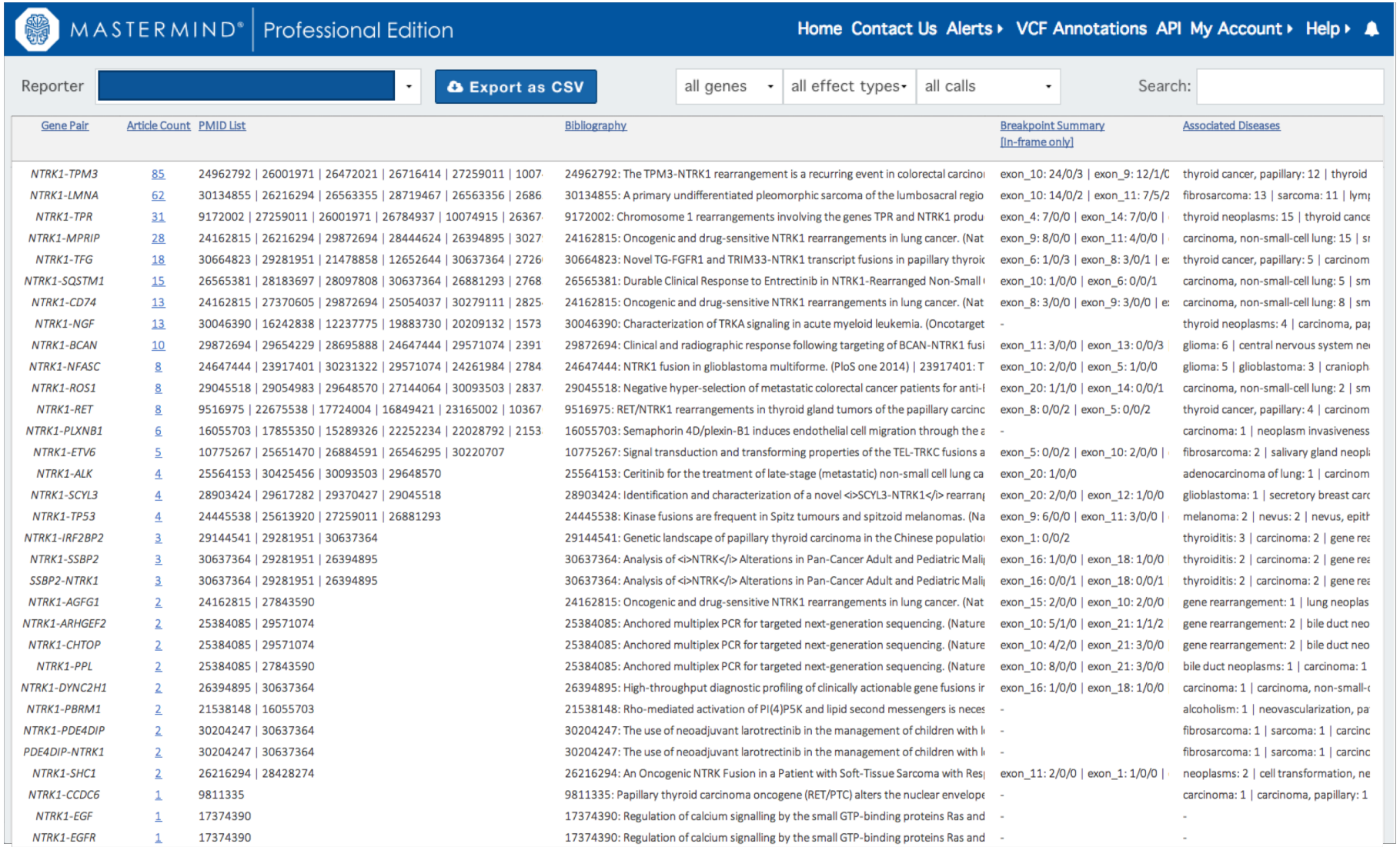
## For 507 Illumina TruSight Fusion genes

- Determine all gene-gene fusions in the medical literature
- Assess the context of these co-mentions at the article- and sentence-levels
- Prioritize by number and strength of these data using internal machine learning techniques
- Annotate for disease, therapies, breakpoints
- Review to identify functional or clinically significant fusion events

*Gene Fusion Database*

# MASTERMIND REPORTER



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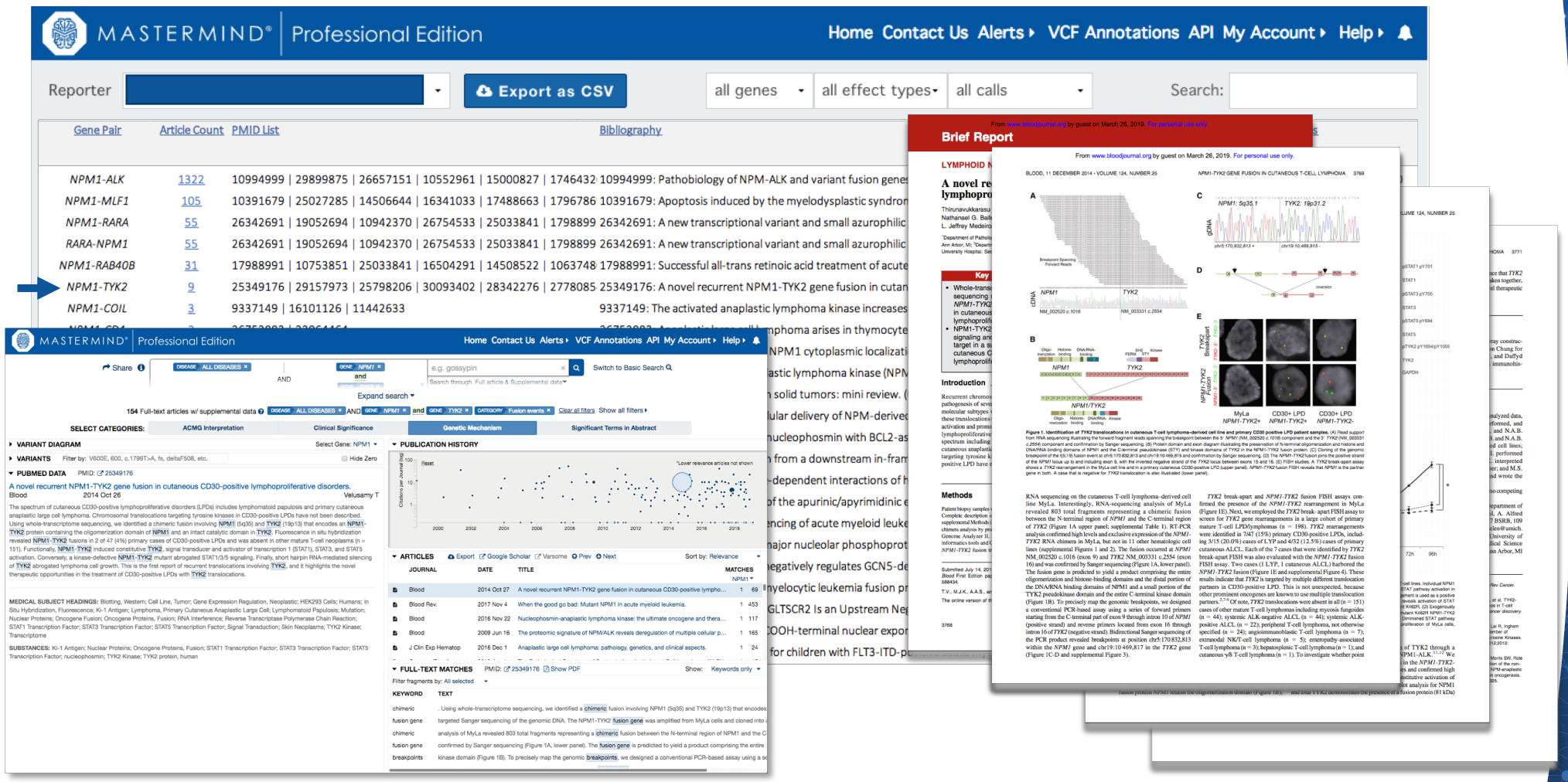
Reporter | Export as CSV | all genes | all effect types | all calls | Search:

| Gene Pair | Article Count | PMID List | Bibliography | Breakpoint Summary [In-frame only] | Associated Diseases |
|---|---|---|---|---|---|
| NTRK1-TPM3 | 85 | 24962792 \| 26001971 \| 26472021 \| 26716414 \| 27259011 \| 1007 | 24962792: The TPM3-NTRK1 rearrangement is a recurring event in colorectal carcino | exon_10: 24/0/3 \| exon_9: 12/1/0 | thyroid cancer, papillary: 12 \| thyroid |
| NTRK1-LMNA | 62 | 30134855 \| 26216294 \| 26563355 \| 28719467 \| 26563356 \| 2686 | 30134855: A primary undifferentiated pleomorphic sarcoma of the lumbosacral regio | exon_10: 14/0/2 \| exon_11: 7/5/2 | fibrosarcoma: 13 \| sarcoma: 11 \| lym |
| NTRK1-TPR | 31 | 9172002 \| 27259011 \| 26001971 \| 26784937 \| 10074915 \| 26367 | 9172002: Chromosome 1 rearrangements involving the genes TPR and NTRK1 produ | exon_4: 7/0/0 \| exon_14: 7/0/0 \| | thyroid neoplasms: 15 \| thyroid cance |
| NTRK1-MPRIP | 28 | 24162815 \| 26216294 \| 29872694 \| 28444624 \| 26394895 \| 3027 | 24162815: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. (Nat | exon_9: 8/0/0 \| exon_11: 4/0/0 \| | carcinoma, non-small-cell lung: 15 \| s |
| NTRK1-TFG | 18 | 30664823 \| 29281951 \| 21478858 \| 12652644 \| 30637364 \| 2726 | 30664823: Novel TG-FGFR1 and TRIM33-NTRK1 transcript fusions in papillary thyroic | exon_6: 1/0/3 \| exon_8: 3/0/1 \| e | thyroid cancer, papillary: 5 \| carcinom |
| NTRK1-SQSTM1 | 15 | 26565381 \| 28183697 \| 28097808 \| 30637364 \| 26881293 \| 2768 | 26565381: Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small | exon_10: 1/0/0 \| exon_6: 0/0/1 | carcinoma, non-small-cell lung: 5 \| sm |
| NTRK1-CD74 | 13 | 24162815 \| 27370605 \| 29872694 \| 25054037 \| 30279111 \| 2825 | 24162815: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. (Nat | exon_8: 3/0/0 \| exon_9: 3/0/0 \| e | carcinoma, non-small-cell lung: 8 \| sm |
| NTRK1-NGF | 13 | 30046390 \| 16242838 \| 12237775 \| 19883730 \| 20209132 \| 1573 | 30046390: Characterization of TRKA signaling in acute myeloid leukemia. (Oncotarget | - | thyroid neoplasms: 4 \| carcinoma, pa |
| NTRK1-BCAN | 10 | 29872694 \| 29654229 \| 28695888 \| 24647444 \| 29571074 \| 2391 | 29872694: Clinical and radiographic response following targeting of BCAN-NTRK1 fusi | exon_11: 3/0/0 \| exon_13: 0/0/3 | glioma: 6 \| central nervous system ne |
| NTRK1-NFASC | 8 | 24647444 \| 23917401 \| 30231322 \| 29571074 \| 24261984 \| 2784 | 24647444: NTRK1 fusion in glioblastoma multiforme. (PloS one 2014) \| 23917401: T | exon_10: 2/0/0 \| exon_5: 1/0/0 | glioma: 5 \| glioblastoma: 3 \| cranioph |
| NTRK1-ROS1 | 8 | 29045518 \| 29054983 \| 29648570 \| 27144064 \| 30093503 \| 2837 | 29045518: Negative hyper-selection of metastatic colorectal cancer patients for anti- | exon_20: 1/1/0 \| exon_14: 0/0/1 | carcinoma, non-small-cell lung: 2 \| sm |
| NTRK1-RET | 8 | 9516975 \| 22675538 \| 17724004 \| 16849421 \| 23165002 \| 10367 | 9516975: RET/NTRK1 rearrangements in thyroid gland tumors of the papillary carcinc | exon_8: 0/0/2 \| exon_5: 0/0/2 | thyroid cancer, papillary: 4 \| carcinom |
| NTRK1-PLXNB1 | 6 | 16055703 \| 17855350 \| 15289326 \| 22252234 \| 22028792 \| 2153 | 16055703: Semaphorin 4D/plexin-B1 induces endothelial cell migration through the a | - | carcinoma: 1 \| neoplasm invasiveness |
| NTRK1-ETV6 | 5 | 10775267 \| 25651470 \| 26884591 \| 26546295 \| 30220707 | 10775267: Signal transduction and transforming properties of the TEL-TRKC fusions a | exon_5: 0/0/2 \| exon_10: 2/0/0 \| | fibrosarcoma: 2 \| salivary gland neopl |
| NTRK1-ALK | 4 | 25564153 \| 30425456 \| 30093503 \| 29648570 | 25564153: Ceritinib for the treatment of late-stage (metastatic) non-small cell lung ca | exon_20: 1/0/0 | adenocarcinoma of lung: 1 \| carcinom |
| NTRK1-SCYL3 | 4 | 28903424 \| 29617282 \| 29370427 \| 29045518 | 28903424: Identification and characterization of a novel SCYL3-NTRK1 rearran | exon_20: 2/0/0 \| exon_12: 1/0/0 | glioblastoma: 1 \| secretory breast carc |
| NTRK1-TP53 | 4 | 24445538 \| 25613920 \| 27259011 \| 26881293 | 24445538: Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. (Na | exon_9: 6/0/0 \| exon_11: 3/0/0 \| | melanoma: 2 \| nevus: 2 \| nevus, epith |
| NTRK1-IRF2BP2 | 3 | 29144541 \| 29281951 \| 30637364 | 29144541: Genetic landscape of papillary thyroid carcinoma in the Chinese populatio | exon_1: 0/0/2 | thyroiditis: 3 \| carcinoma: 2 \| gene re |
| NTRK1-SSBP2 | 3 | 30637364 \| 29281951 \| 26394895 | 30637364: Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Mali | exon_16: 1/0/0 \| exon_18: 1/0/0 | thyroiditis: 2 \| carcinoma: 2 \| gene re |
| SSBP2-NTRK1 | 3 | 30637364 \| 29281951 \| 26394895 | 30637364: Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Mali | exon_16: 0/0/1 \| exon_18: 0/0/1 | thyroiditis: 2 \| carcinoma: 2 \| gene re |
| NTRK1-AGFG1 | 2 | 24162815 \| 27843590 | 24162815: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. (Nat | exon_15: 2/0/0 \| exon_10: 2/0/0 | gene rearrangement: 1 \| lung neoplas |
| NTRK1-ARHGEF2 | 2 | 25384085 \| 29571074 | 25384085: Anchored multiplex PCR for targeted next-generation sequencing. (Nature | exon_10: 5/1/0 \| exon_21: 1/1/2 | gene rearrangement: 2 \| bile duct neo |
| NTRK1-CHTOP | 2 | 25384085 \| 29571074 | 25384085: Anchored multiplex PCR for targeted next-generation sequencing. (Nature | exon_10: 4/2/0 \| exon_21: 3/0/0 | gene rearrangement: 2 \| bile duct neo |
| NTRK1-PPL | 2 | 25384085 \| 27843590 | 25384085: Anchored multiplex PCR for targeted next-generation sequencing. (Nature | exon_10: 8/0/0 \| exon_21: 3/0/0 | bile duct neoplasms: 1 \| carcinoma: 1 |
| NTRK1-DYNC2H1 | 2 | 26394895 \| 30637364 | 26394895: High-throughput diagnostic profiling of clinically actionable gene fusions ir | exon_16: 1/0/0 \| exon_18: 1/0/0 | carcinoma: 1 \| carcinoma, non-small- |
| NTRK1-PBRM1 | 2 | 21538148 \| 16055703 | 21538148: Rho-mediated activation of PI(4)P5K and lipid second messengers is neces | - | alcoholism: 1 \| neovascularization, pa |
| NTRK1-PDE4DIP | 2 | 30204247 \| 30637364 | 30204247: The use of neoadjuvant larotrectinib in the management of children with l | - | fibrosarcoma: 1 \| sarcoma: 1 \| carcinc |
| PDE4DIP-NTRK1 | 2 | 30204247 \| 30637364 | 30204247: The use of neoadjuvant larotrectinib in the management of children with l | - | fibrosarcoma: 1 \| sarcoma: 1 \| carcinc |
| NTRK1-SHC1 | 2 | 26216294 \| 28428274 | 26216294: An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Res | exon_11: 2/0/0 \| exon_1: 1/0/0 \| | neoplasms: 2 \| cell transformation, ne |
| NTRK1-CCDC6 | 1 | 9811335 | 9811335: Papillary thyroid carcinoma oncogene (RET/PTC) alters the nuclear envelope | - | carcinoma: 1 \| carcinoma, papillary: 1 |
| NTRK1-EGF | 1 | 17374390 | 17374390: Regulation of calcium signalling by the small GTP-binding proteins Ras and | - | - |
| NTRK1-EGFR | 1 | 17374390 | 17374390: Regulation of calcium signalling by the small GTP-binding proteins Ras and | - | - |

*Gene Fusion Database*

# MASTERMIND REPORTER



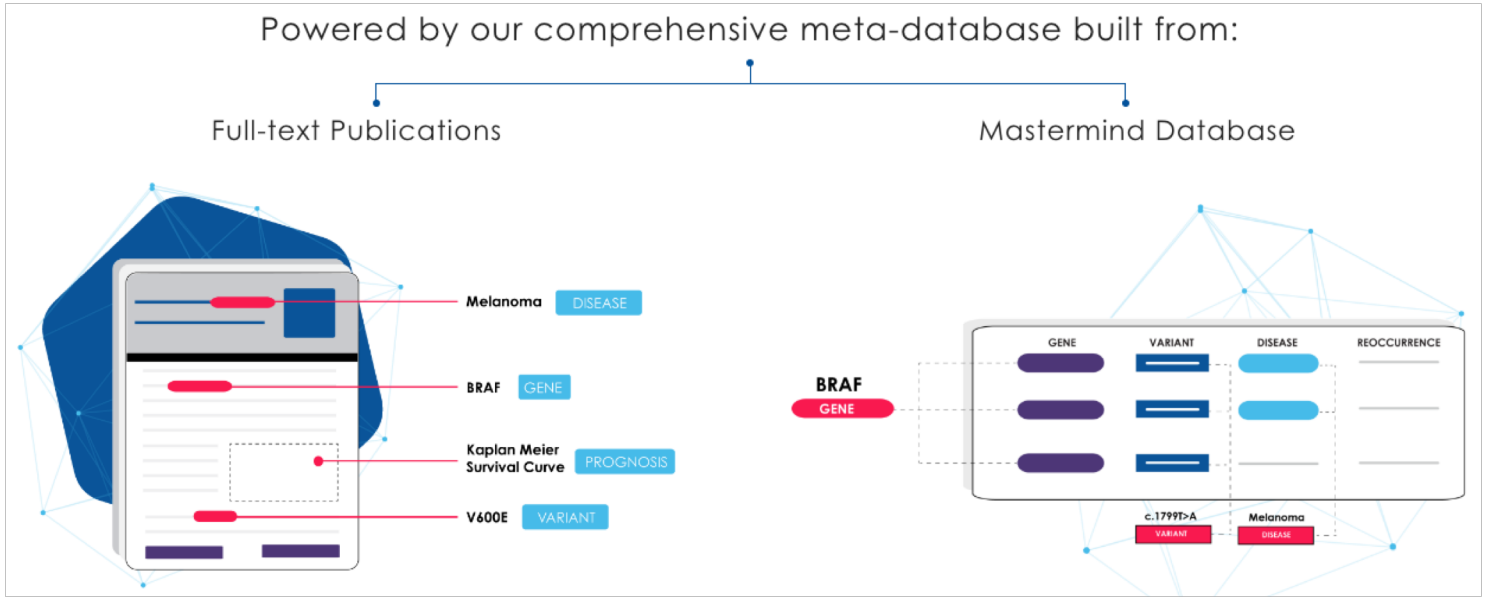
# REPRESENTATIVE USE CASE DESCRIPTIONS

- Clinical reporting on patient RNAseq data
- Annotation of TCGA or other clinical database data
- Patient selection for clinical trials
- Uncovering novel fusion mechanisms to inform pharma R+D

# MASTERMIND GENOMIC DATABASE

*Comprehensive Index of the Genomic Literature*

*Annotated for Clinical and Functional Variants*




**30M**

TITLES/ABSTRACTS SCANNED

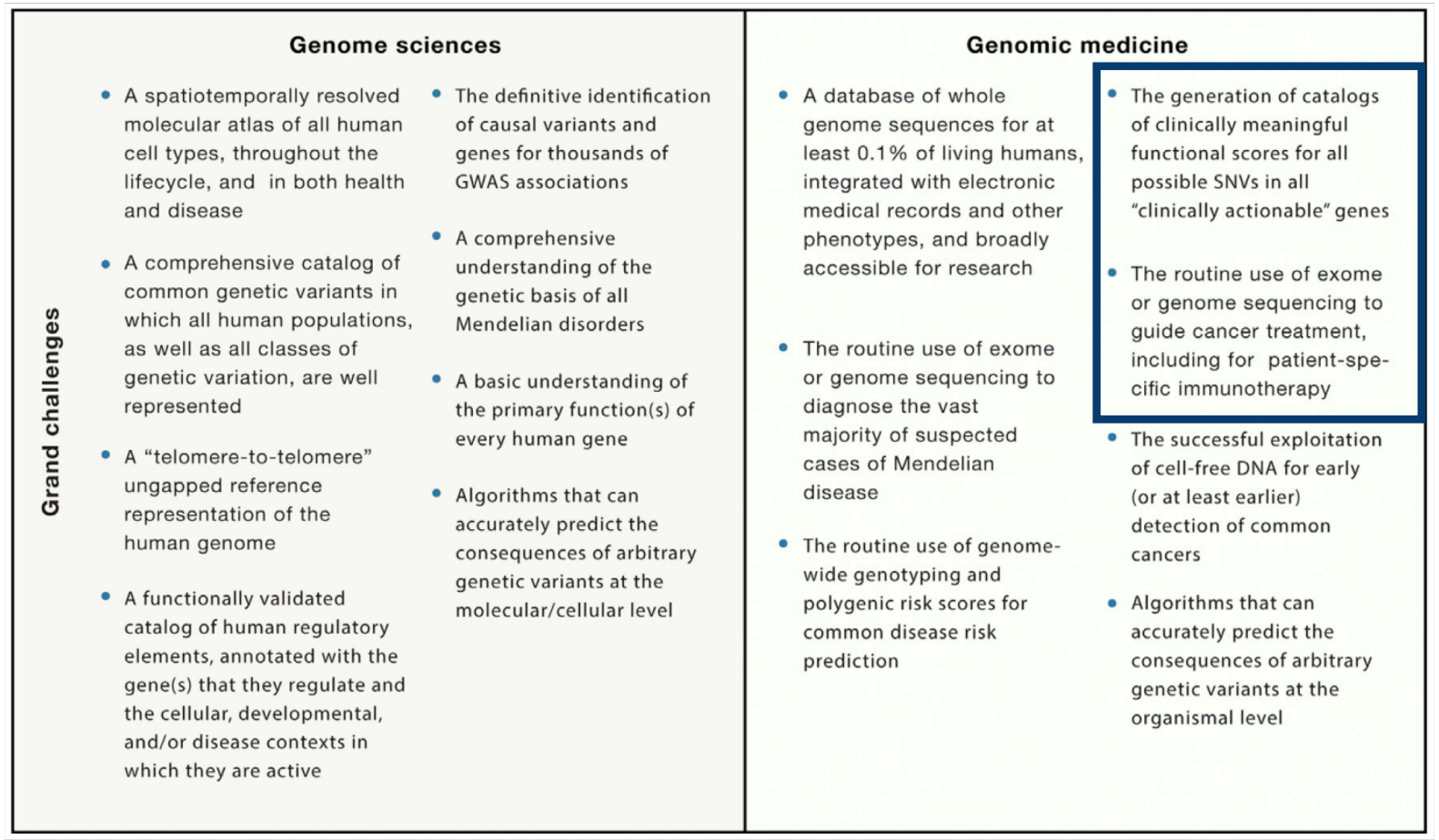
**6.2M**

FULL-TEXT GENOMIC ARTICLES INDEXED

**10K Diseases**
**20K Genes**
**4.1M Variants**

*Genomenon's Mission*

# COMPREHENSIVE GENOMIC UNDERSTANDING



| Grand challenges | Genome sciences | Genomic medicine |
|---|---|---|
| | • A spatiotemporally resolved molecular atlas of all human cell types, throughout the lifecycle, and in both health and disease | • The definitive identification of causal variants and genes for thousands of GWAS associations |
| | • A comprehensive catalog of common genetic variants in which all human populations, as well as all classes of genetic variation, are well represented | • A comprehensive understanding of the genetic basis of all Mendelian disorders |
| | • A "telomere-to-telomere" ungapped reference representation of the human genome | • A basic understanding of the primary function(s) of every human gene |
| | • A functionally validated catalog of human regulatory elements, annotated with the gene(s) that they regulate and the cellular, developmental, and/or disease contexts in which they are active | • Algorithms that can accurately predict the consequences of arbitrary genetic variants at the molecular/cellular level |
| | • A database of whole genome sequences for at least 0.1% of living humans, integrated with electronic medical records and other phenotypes, and broadly accessible for research | • The generation of catalogs of clinically meaningful functional scores for all possible SNVs in all "clinically actionable" genes |
| | • The routine use of exome or genome sequencing to diagnose the vast majority of suspected cases of Mendelian disease | • The routine use of exome or genome sequencing to guide cancer treatment, including for patient-specific immunotherapy |
| | • The routine use of genome-wide genotyping and polygenic risk scores for common disease risk prediction | • The successful exploitation of cell-free DNA for early (or at least earlier) detection of common cancers |
| | | • Algorithms that can accurately predict the consequences of arbitrary genetic variants at the organismal level |

1. Single Nucleotide Variants
2. Small Indels
3. Copy Number Variants
4. Fusion Events ←

*Genomic Medicine – Progress, Pitfalls, Promise*. Shendure et al. 2019. PMID 30901547

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# Thank You

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