# Assessing the Economics of Genomic Medicine

Kenneth Offit, MD MPH
Chief, Clinical Genetics Service
Memorial Sloan-Kettering Cancer Center

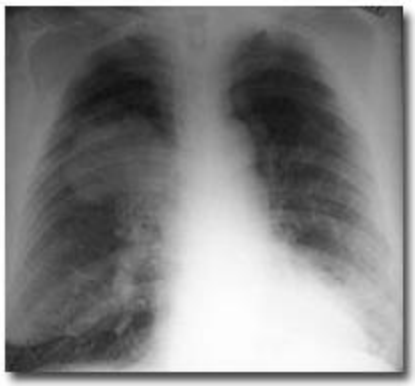
- **DISCLOSURES**

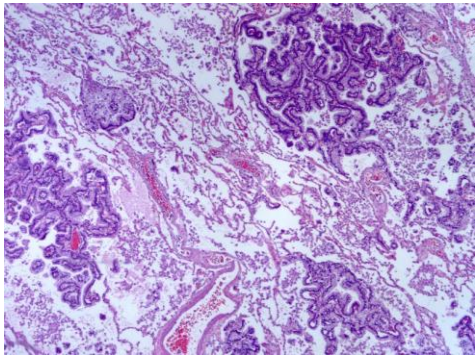
- **No conflicts**
- **Patents unenforced**
- **Consultancies unpaid**
- **ASCO volunteer**
- **Government advisory Committees (EGAPP, NCI BSC)**

*"It is thornlike in appearance, but I need to order a battery of tests."*

# Scenario

- The individual presents at age 50 with cough, dyspnea, and chest discomfort. Evaluation reveals a lung mass; bronchoscopy and biopsy reveals *advanced* non-small cell lung cancer. Her tumor is found to have variations that allow the use of targeted therapy and with treatment the patient goes into remission, *followed by relapse, further testing and treatment.*

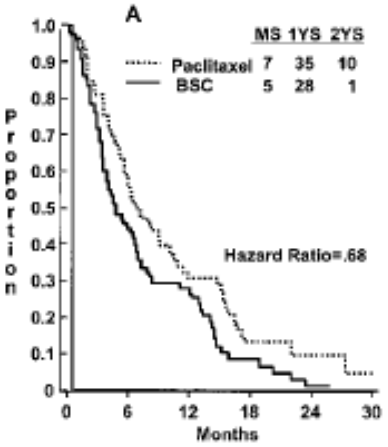




# Cancer Clinical Scenario Conclusions

- Model 1 (targeted mutation testing):
  - Current Practice
  - Resistance
  - Companion Diagnostics
- Model 2 (MPS for disease and actionable variants):
  - More genomes in Oncology than anywhere else
  - More germline genomes also, (including PG), not fully exploited
- Model 3 (MPS + incidentaloma with no threshold):
  - Genomes give more information than exomes
  - Full disclosure of "incidentalome" a research question (45 CFR)

Standard chemotherapy (2001)




| First Author (ref) | Therapy | No. of Patients | OR (%) | Median Survival (months) |
|---|---|---|---|---|
| Kelly (SWOG)[24] | Vinorelbine/cisplatin | 202 | 29 | 8 |
| | Paclitaxel/carboplatin | 206 | 25 | 8 |
| Schiller (ECOG)[25] | Paclitaxel/cisplatin | 292 | 21 | 7.8 |
| | Gemcitabine/cisplatin | 288 | 21 | 8.1 |
| | Docetaxel/cisplatin | 293 | 17 | 7.4 |
| | Paclitaxel/carboplatin | 299 | 15 | 8.2 |

TKI as Second Line chemotherapy (2003)

JAMA The Journal of the American Medical Association

Home Current Issue All Issues Online First Specialties & Topics CME Multin

October 22/29, 2003, Vol 290, No. 16 >

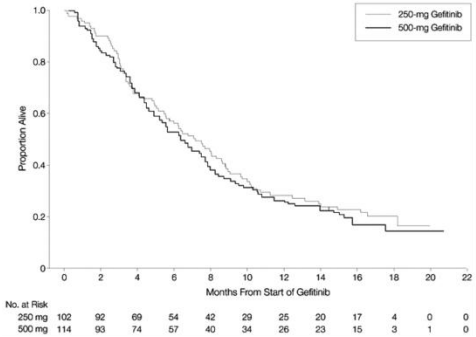
< Previous Article Next Article >

Original Contribution | October 22/29, 2003

**Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients With Non–Small Cell Lung Cancer**

**A Randomized Trial** FREE

Mark G. Kris, MD; Ronald B. Natale, MD; Roy S. Herbst, MD; Thomas J. Lynch, Jr, MD; Diane Prager, MD; Chandra




Targeting of TKI (2004)

**EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib**

William Pao*†‡, Vincent Miller†§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†§, and Harold Varmus*

*Program in Cancer Biology and Genetics and Departments of †Medicine, ‖Surgery, ¶Pathology, and **Radiology, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; and ††Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Boulevard,

75-82% RR

PFS 8.9-13.3 mos

Resistance to TKI (2006)

*Cancer Therapy: Clinical*

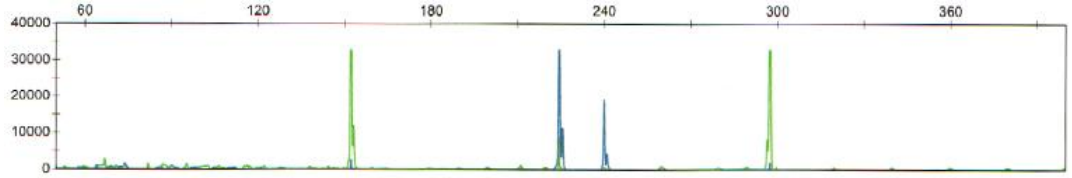
**Novel D761Yand Common Secondary T790M Mutations in Epidermal Growth Factor Receptor–Mutant Lung Adenocarcinomas with Acquired Resistance to Kinase Inhibitors**

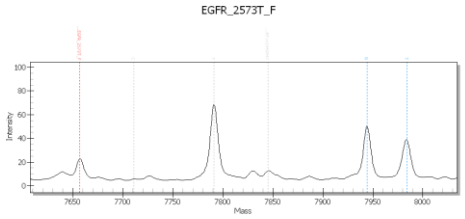
Marissa N. Balak,[1] Yixuan Gong,[1] Gregory J. Riely,[2] Romel Somwar,[3] Allan R. Li,[4] Maureen F. Zakowski,[4] Anne Chiang,[2] Guangli Yang,[5] Ouathek Ouerfelli,[5] Mark G. Kris,[2,6] Marc Ladanyi,[1,4] Vincent A. Miller,[2,6] and William Pao[1,2,6]

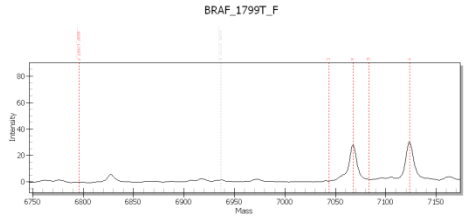
# Model 1: Targeted panels today

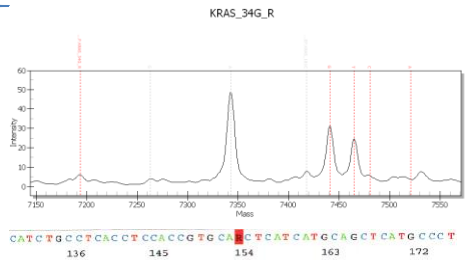
- Lung adenocarcinoma
  - EGFR exon 19
  - EGFR exon 20
  - ERBB2 exon 20
  - EGFR exon 21
  - PIK3CA
  - BRAF
  - KRAS
  - EGFR T790M
  - EML4-ALK
  - MET
  - ROS

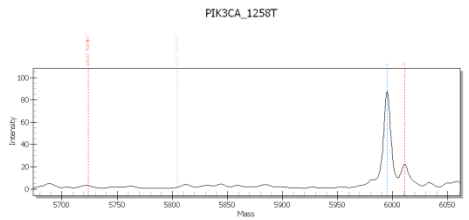
EGFR exon 20 | EGFR exon 19 | ERBB2 exon 20

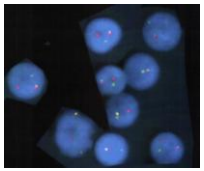


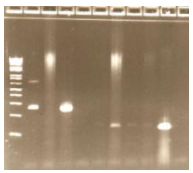



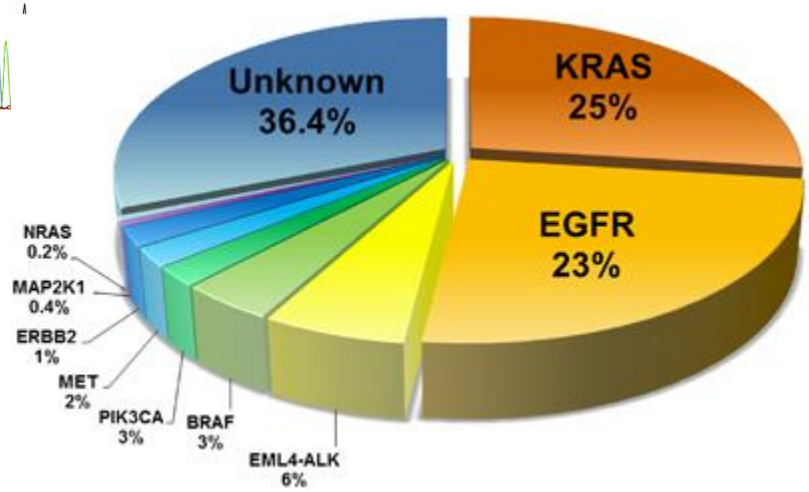








MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

# Targeted therapies approved or in pre-clinical study for lung cancer

| Target | Clinically Approved for Lung Cancer | In Clinical Trials for Lung Cancer | Novel Agents in Preclinical Study |
|---|---|---|---|
| EGFR | Erlotinib, cetuximab * | Afatinib (BIBW 2992), BMS-690514, canertinib, CUDC-101, EKB-569, gefitinib †, icotinib, lapatinib, matuzumab, necitumumab, neratinib (HKI-272), nimotuzumab, panitumumab, pelitinib, PF0299804, vandetanib, XL647, zalutumumab | AEE 788, AV-412, BMS-599626 |
| VEGFR | | Axitinib, BMS-690514, brivanib alaninate (BMS-582664), cediranib, E7080, foretinib, linifanib, motesanib (AMG-706), neovastat (AE-941), pazopanib, ramucirumab, regorafenib, sorafenib, sunitinib, tivozanib, vandetanib, vargatef (BIBF 1120), vatalanib, XL184, XL647, XL999 | Adnectin, AEE 788, TKI-258, TSU-68 |
| ALK | Crizotinib | | GSK1838705A, nVP-TAE684 |
| HER2 | | Afatinib (BIBW 2992), BMS-690514, CI-1033, CUDC-101, EKB-569, lapatinib, PF0299804, neratinib (HKI-272), pertuzumab, trastuzumab, XL647 | AEE 788, AV-412, BMS-599626 |
| c-MET | Crizotinib | AMG 102, AV-299 (SCH-900105), foretinib, GSK1363089, MetMAb, tivantinib (ARQ197), XL184 | AMG 208, PF-04217903, PHA-665752, SGX523, SU11274 |
| PDGFR | | Axitinib, cediranib, dasatinib (BMS-354825), E7080, imatinib, IMC-3G3, linifanib, motesanib (AMG-706), pazopanib, ramucirumab, regorafenib, sorafenib, sunitinib, vargatef (BIBF 1120), vatalanib, XL999 | TKI-258, TSU-68 |
| IGF-1R | | AMG 479, BIIB022, cixutumumab (IMC-A12), figitumumab (CP751,851), MK-0646, OSI906 | BMS-754807 |
| FGFR | | Brivanib alaninate (BMS-582664), E-7080, regorafenib, vargatef (BIBF 1120), XL999 | FP-1039, PD-173074, TKI-258, TSU-68 |
| c-KIT | | Axitinib, cediranib, dasatinib (BMS-354825), imatinib, motesanib (AMG-706), pazopanib, regorafenib, sorafenib, sunitinib, vatalanib | |
| FLT-3 | | MK0457, sorafenib, sunitinib, XL999 | |
| SRC/BCR-ABL | | AZD0530, dasatinib (BMS-354825), imatinib, XL999 | KX2-391 |
| DDR2 | | Dasatinib (BMS-354825) | |

| Pathway | Target | Clinically Approved for Lung Cancer | In Clinical Trials for Lung Cancer | Novel Agents in Preclinical Study |
|---|---|---|---|---|
| Angiogenesis | VEGF | Bevacizumab | Aflibercept (AVE005), AMG706, cediranib (AZD2171) | |
| RAS/RAF/ MEK/ERK | RAS | | Lonafarnib, tipifarnib | ISIS 2503 (H-ras) |
| | RAF | | GSK2118436, regorafenib, sorafenib | AZ628, ISIS 5132, XL281 (BMS-908662) |
| | MEK | | GSK1120212, PD325901, selumetinib (AZD6244), sorafenib | AS 703026, AZD8330, GDC-0973, RDEA119 |
| PI3K/AKT/mTOR | PI3K | | BKM120, GDC-0941, PX-866, XL147, XL765 | BEZ235, BGT226, LY294002 |
| | AKT | | Nelfinavir, MK-2206, perifosine | |
| | mTOR | | Everolimus (RAD001), PX-866, ridaforolimus, sirolimus/rapamycin, temsirolimus (CCI-779) | AZD8055, BEZ235, OSI-027 |
| Apoptosis | IAPs | | | HGS1029 |
| | TRAIL | | Conatumumab (AMG 655), dulanermin (AMG 951), mapatumumab | Apomab, lexatumumab |
| | BCL2 | | Gossypol, navitoclax (ABT-263), oblimersen, obatoclax | ABT-737 |
| | PARP | | Iniparib (SAR240550), veliparbi | AG014699, olaparib FUS1 Fus1 liposome complex |
| HSPs | HSP90 | | Ganetespib (STA-9090), retaspimycin (IPI-504), SNX-5422 (PF04929113), tanespimycin | 17-AAG, alvespimycin |
| HDACs | HDACs | | Belinostat, CI-994 (tacedinaline), CUDC-101, entinostat, panobinostat (LBH589), Pivanex, romidepsin, vorinostat | SB939 |
| Proteosome | Proteosome | | Carfilzomib, bortezomib, salinosporamide A (NPI-0052) | CEP-18770, MLN9708 |
| Stem cell pathways | Hh (SMO) | | RO4929097, vismodegib (GDC-0449), XL139 (BMS-833923) | Cyclopamine, IPI-926, LDE225 |
| | Notch (γ-secretase) | | | MK0752, MRK-003, PF03084014 |
| Telomerase | Telomerase | | Imetelstat (GRN-163L), KML-001 (sodium meta-arsenite) | Sodium meta-arsenite |
| Cell cycle/cell proliferation | p53 | | | p53 peptide vaccine, PRIMA-1 |
| | MDM2 | | | JNJ-26854165, RO5045337 |

# RTK, ALK, QALY

**Economic Analysis: Randomized Placebo-Controlled Clinical Trial of Erlotinib in Advanced Non–Small Cell Lung Cancer**

Penelope A. Bradbun
Ming-Sound Tsao, Willi
Group on Economic Ar

Manuscript received M

Correspondence to: Natasl

Results The increme
year gained
magnitude
cost-effectiv

J Natl Cancer

British Journal of Cancer (2012) 106, 1100 – 1106

www.bjcancer.com

The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers

**AJ Atherly[1] and DR Camidge[*,2]**

*[1]Department of Health Systems, Management and Policy, Colorado School of Public Health, University of Colorado, Aurora, CO, USA; [2]Division of Medical Oncology, University of Colorado Cancer Center, Anschutz Medical Campus, Anschutz Cancer Pavillion, Mailstop F704, 1665 North Aurora Court, Aurora 80045, CO, USA*

RESULTS: For assays costing $1
NSCLC, excluding treatment c
biomarker frequency from 1.6
unscreened group. Cheaper scr
exceed proportion of subjects
effect of screening cost per p
achievable at biomarker freque

| Targeted Genetic Intervention | Cost per QALY |
|---|---|
| Lung /Erlotinib | $94,638 |
| Lung /ALK | $106,707 |
| **BRCA1* testing/MRI age 35-54 | $55,420 |
| ***Lynch/IHC/*BRAF* | $36,200 |
| *JAMA 295:2374, 2006<br>**Ann Int Med 155:69, 2011 | |

# Exploiting Genetics of Resistence

Table 1

**Overview of recently developed, genotype-guided, molecularly targeted cancer therapies and associated mechanisms of acquired drug resistance**

| Target | Drug | Acquired resistance mechanism (pre-clinical) | Acquired resistance mechanism (clinical) |
|---|---|---|---|
| EGFR | Gefitinib, erlotinib | *EGFR* T790M, *MET* amplification, IGF1R activation, EMT, reversible epigenetic | *EGFR* T790M, *MET* amplification, EMT, small cell differentiation |
| BRAF | Vemurafenib | CRAF elevation, *BRAF* amplification, COT1 elevation PDGFRB elevation, IGF1R elevation | *NRAS* mutation, *MEK* mutation, PDGFRB elevation, COT1 elevation |
| ALK | Crizotinib | *EGFR* activation, *ALK* secondary mutation | *EGFR* activation, *ALK* secondary mutation |
| SMO | Vismodegib, NVP-LDE225 | *SMO* mutation, *Gli2* amplification, PI3K elevation | *SMO* mutation |
| PARP | Olaparib, iniparib, veniparib | *BRCA2* intragenic deletion | None |
| JAK1,2 | Several | None | None |

Current Opinion in Genetics & Development 2012, 22:45–49

# Woops, the tumor may show hallmarks of germline changes: the example of *EGFR*T790M*

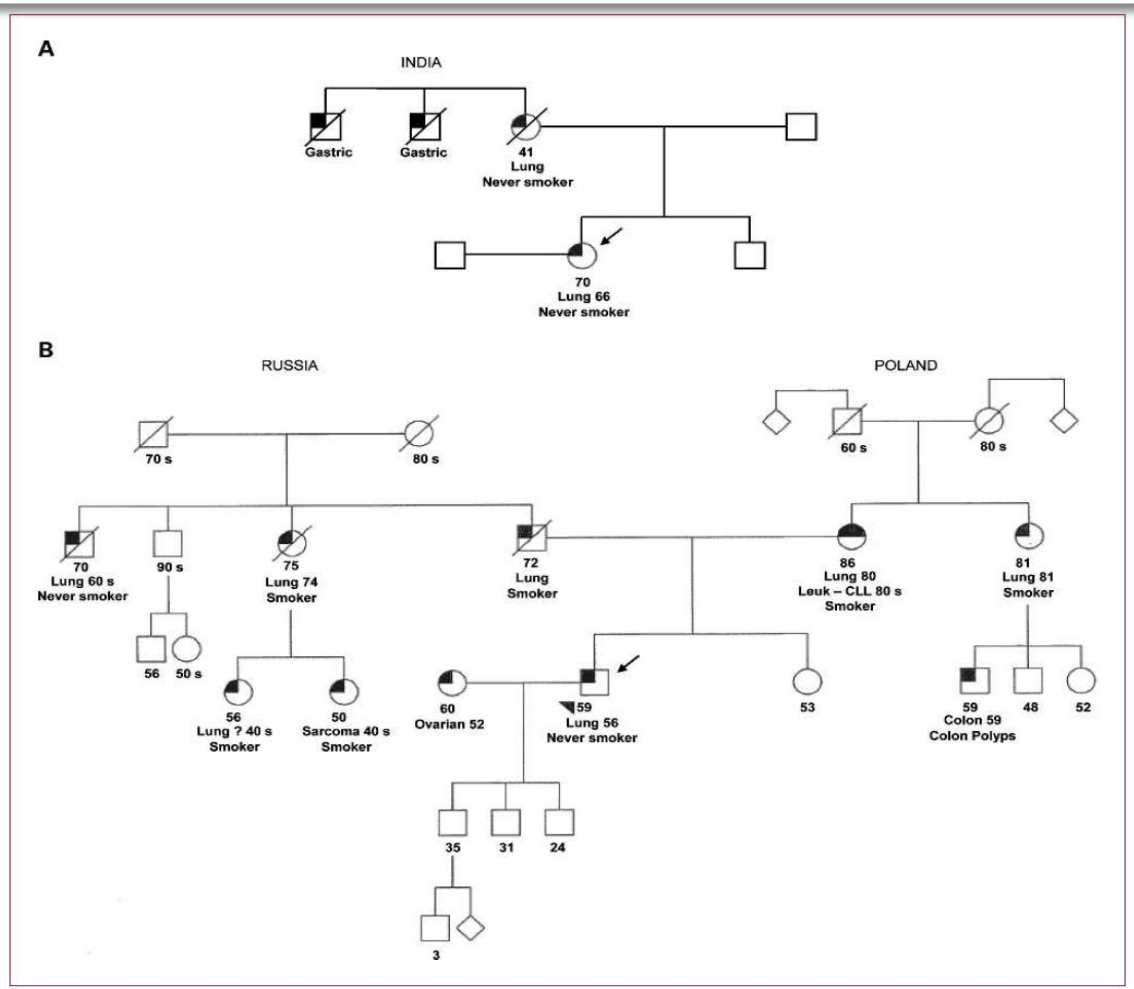



Fig. 3. Pedigrees of patients found to have a germ line *EGFR* T790M mutation. Numbers, ages of family members; arrows, probands; Lung, patients with lung cancer (followed by age at onset); Leuk, leukemia; CLL, chronic lymphoid leukemia; Gastric, gastric cancer.

PHYSORG.com
SCIENCE : PHYSICS : TECH : NANO : NEWS

CT screening reduces lung-cancer deaths in heavy smokers

**(PhysOrg.com) -- Studying heavy smokers, the National Cancer Institute’s 33-center National Lung Screening Trial found that significantly fewer who were screened with low-dose CT scans died from lung cancer than heavy smokers screened with standard chest X-rays.**

The study involved more than 53,000 people in the United States, including more than 3,800 participants at the Washington University School of Medicine and Barnes-Jewish Hospital.

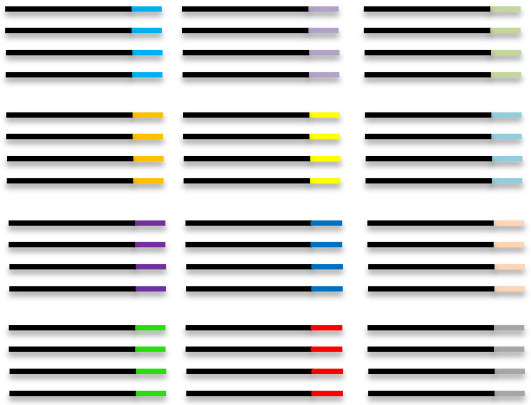
*JAMA*. 2012;307(22):2418-2429

- Girard et al *Clin Cancer Res.* 2010 Jan 15;16(2):755-63

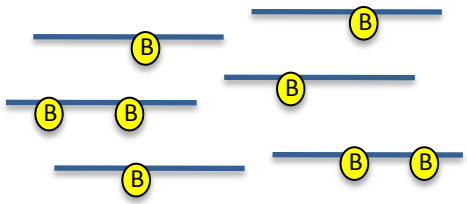
# Model 2: Sequencing of "Actionable"Cancer Genes

**IMPACT**: Integrated Mutation Profiling of Actionable Cancer Targets

Prepare **12-24 libraries**

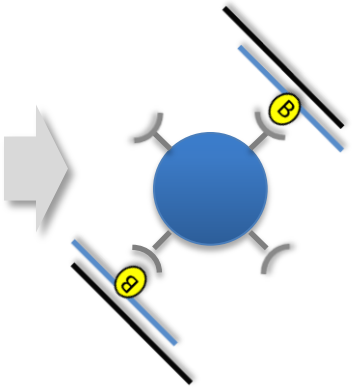


Baits for **230 cancer genes**




*Berger Lab*

Hybridize and select (NimbleGen SeqCap)

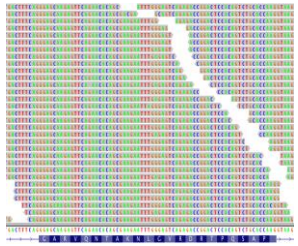



*Berger Lab*

Sequence to 500-1000X (1 lane of HiSeq 2000)

*Genomics Core Lab*

Align to genome and analyze



*Berger Lab*

adapted from *Wagle, Berger et al., Cancer Discovery, 2:82-93, January 2012*

# Current List of 230 Cancer Genes

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ABL1 | CBLC | DNMT1 | FGFR1 | IGF1R | MDM2 | NOTCH2 | PNRC1 | SPOP |
| ABL2 | CCND1 | DNMT3A | FGFR2 | IGFBP7 | MDM4 | NOTCH3 | PREX2 | SRC |
| AKT1 | CCNE1 | DNMT3B | FGFR3 | IKBKE | MEN1 | NOTCH4 | PRKAR1A | STK11 |
| AKT2 | CD79B | EGFR | FGFR4 | IKZF1 | MET | NPM1 | PRKCI | SUFU |
| AKT3 | CDC42EP2 | EIF4EBP1 | FH | INSR | MITF | NRAS | PTCH1 | TBK1 |
| ALK | CDC73 | EP300 | FLCN | IRS1 | MLH1 | NTRK1 | PTEN | TEK |
| ALOX12B | CDH1 | EPHA3 | FLT1 | IRS2 | MLL | NTRK2 | PTPN11 | TERT |
| APC | CDK4 | EPHA5 | FLT3 | JAK1 | MLL2 | NTRK3 | PTPRD | TET1 |
| AR | CDK6 | EPHA6 | FOXL2 | JAK2 | MLL3 | PAK7 | PTPRS | TET2 |
| ARAF | CDK8 | EPHA7 | GATA1 | JAK3 | MLST8 | PARK2 | RAF1 | TGFBR2 |
| ARHGAP26 | CDKN2A | EPHA8 | GATA2 | JUN | MPL | PARP1 | RARA | TMPRSS2 |
| ARID1A | CDKN2B | EPHB1 | GATA3 | KDM5C | MSH2 | PAX5 | RB1 | TNFAIP3 |
| ASXL1 | CDKN2C | EPHB4 | GNA11 | KDM6A | MSH6 | PBRM1 | REL | TOP1 |
| ATM | CEBPA | EPHB6 | GNAQ | KDR | MTOR | PDGFRA | RET | TP53 |
| ATRX | CHEK1 | ERBB2 | GNAS | KEAP1 | MYB | PDGFRB | RICTOR | TP63 |
| AURKA | CHEK2 | ERBB3 | GOLPH3 | KIT | MYC | PHOX2B | RPTOR | TSC1 |
| BAP1 | CREBBP | ERBB4 | GRIN2A | KLF6 | MYCL1 | PIK3C2G | RUNX1 | TSC2 |
| BCL2L1 | CRKL | ERG | GSK3B | KRAS | MYCN | PIK3CA | SDHB | TSHR |
| BCL6 | CRLF2 | ESR1 | HDAC2 | LDHA | NCOA2 | PIK3CB | SETD2 | VHL |
| BIRC2 | CSF1R | ETV1 | HIF1A | LGR6 | NF1 | PIK3CD | SHQ1 | WT1 |
| BRAF | CTNNB1 | ETV6 | HMGA2 | MAGI2 | NF2 | PIK3CG | SMAD4 | YAP1 |
| BRCA1 | CYLD | EZH2 | HNF1A | MAP2K1 | NFE2L2 | PIK3R1 | SMARCA4 | YES1 |
| BRCA2 | DAXX | FAM123B | HRAS | MAP2K2 | NFKB1 | PIK3R2 | SMARCB1 | |
| CARD11 | DDR2 | FAM46C | HSP90AA1 | MAP2K4 | NFKB2 | PIK3R3 | SMO | |
| CBL | DICER1 | FAS | IDH1 | MAP3K8 | NKX2-1 | PKM2 | SOCS1 | |
| CBLB | DIS3 | FBXW7 | IDH2 | MCL1 | NOTCH1 | PLK2 | SOX2 | |

*Caveats:*
*-VUS!*
*- consent*

# When lawyers write consents for commercial (for-profit) NGS

Ambry Genetics™

## Exome Requisition - Proband (requisition and consent)

*Required for processing

### 4b. OPTION FOR RESULTS BLINDING (LATER-ONSET DISEASE) *[Skip if <18 y.o.]*

Later-onset disease: A mutation may increase the risk of developing a particular disease. An individual may carry a mutation but not yet have symptoms of this disease. This can be because symptoms usually begin at an age older than the individual has currently attained. These diseases also may not be fully penetrant; that is, often a mutation in one of these genes may simply increase individual risk of disease but does not predict the onset of disease with certainty. For example: A 40-year-old man is found to carry a mutation in a gene which increases the risk of dementia. He is in excellent health and has no problems with memory or cognition. This may be because the individual will develop symptoms at a later age (50's or 60's) or this individual may never develop symptoms (not penetrant).

In some cases, preventative treatment may be available to prevent or slow the onset of symptoms. Some of these disorders would include: Alzheimers disease, Parkinsons disease, polycystic kidney disease, hypertrophic cardiomyopathy, and many more.

This information may impact personal health (choose one):

☐ I choose to receive information regarding risk for later-onset disease.

_____ ☐ However, there are specific genes or conditions for which I DO NOT want to receive information (indicate them below or attached additional sheet).
*(Initial here)*

_____

☐ I choose NOT to receive information regarding risk for later-onset disease.

_____ ☐ However, there are specific genes or conditions for which I DO want to receive information (indicate them below or attached additional sheet).
*(Initial here)*

_____

# When Academics write Consent for Research NGS

**UNIVERSITY OF MICHIGAN**

**CONSENT TO BE PART OF A RESEARCH STUDY**

Please feel free to ask questions and discuss your preferences with the study team members. They will help you complete the table. If you do nothing, you will be told. However, if you wish not to be told, please initial where indicated below.

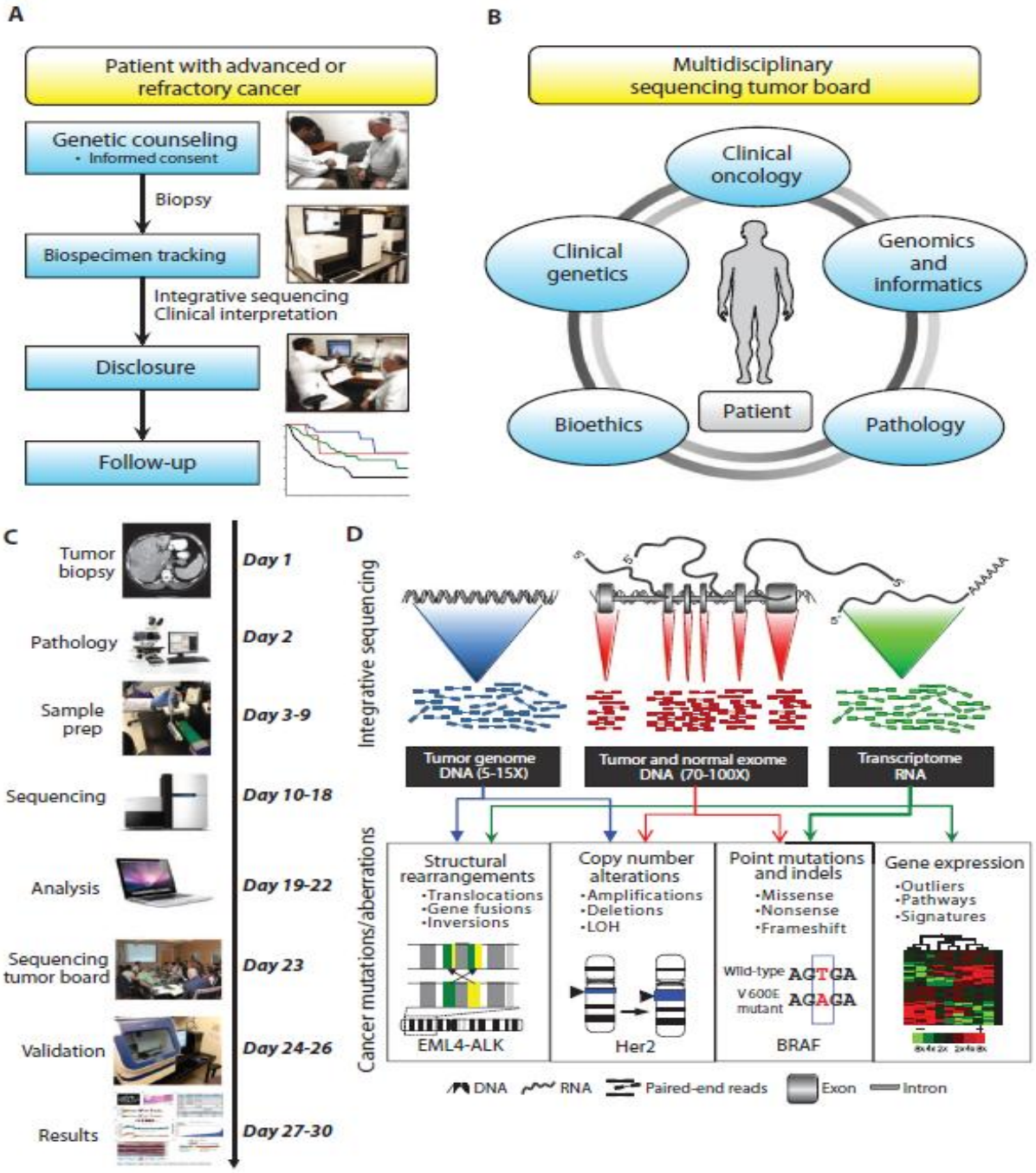
| **What choices do I have for receiving these other results that do not have direct impact on care of my current cancer?** | **If you do NOT want to be told of these results, please initial the boxes below.** |
|---|---|
| 1) Results that may have **significance for biological family members**. | |
| 2) Results that are **not related to your cancer,** but may have **potential medical impact for you**. | |

**5.2 What are the risks of genetic research?**

There are some risks to receiving genetic results. Participants could experience risks such as psychological or emotional distress, loss of insurance, loss of employment, discovery of previously unknown health conditions, discovery that you are not the biological parent of a child(ren), or discovery that you could carry a gene for a certain disease, etc. Therefore, we offer **genetic counseling** before participation in the study as part of the informed consent process.

Science Translational Medicine AAAS

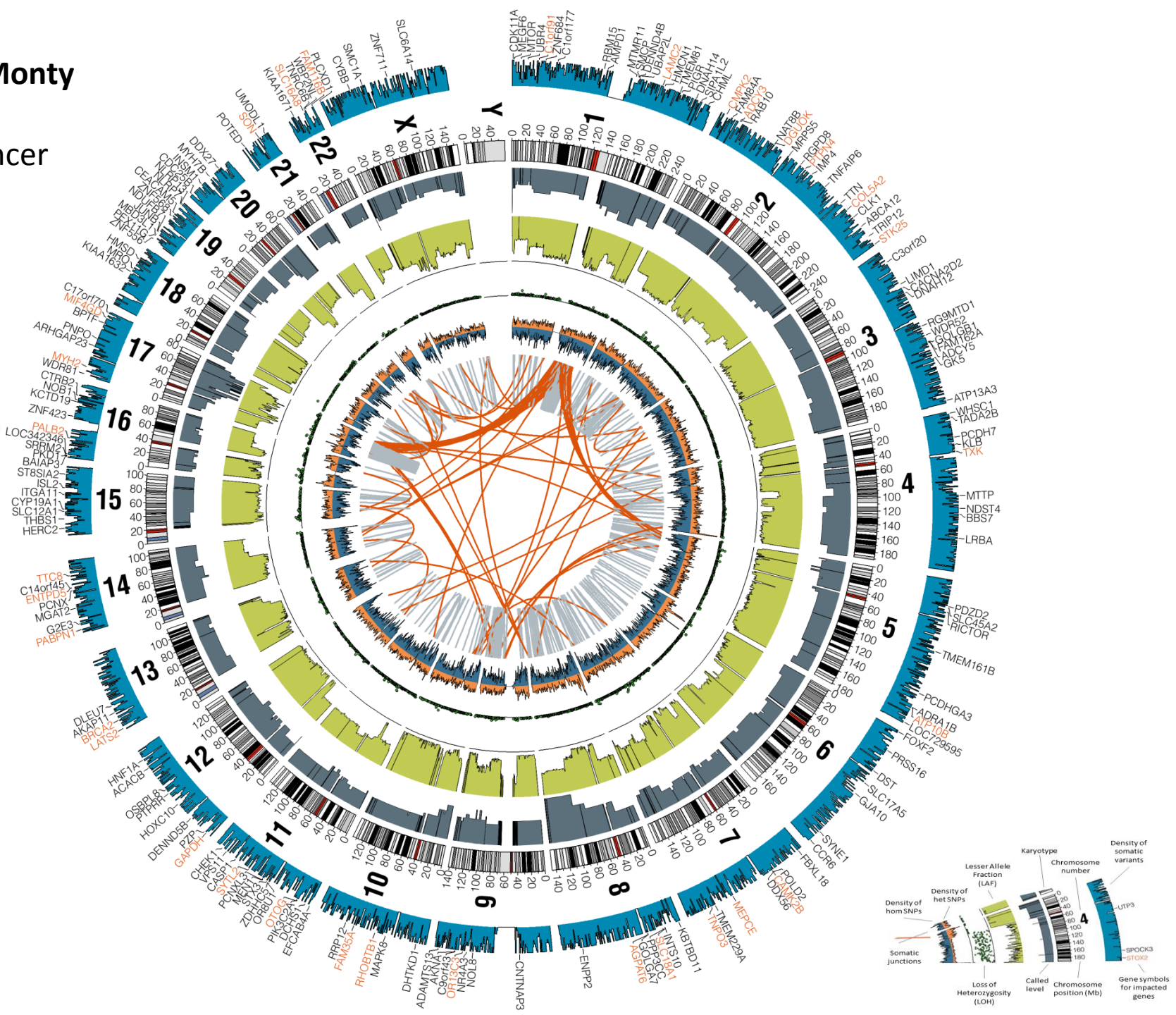
**Personalized Oncology Through Integrative High-Throughput Sequencing: A Pilot Study**
Sameek Roychowdhury *et al.*
*Sci Transl Med* 3, 111ra121 (2011);
DOI: 10.1126/scitranslmed.3003161



# Model 3
# The Full Monty

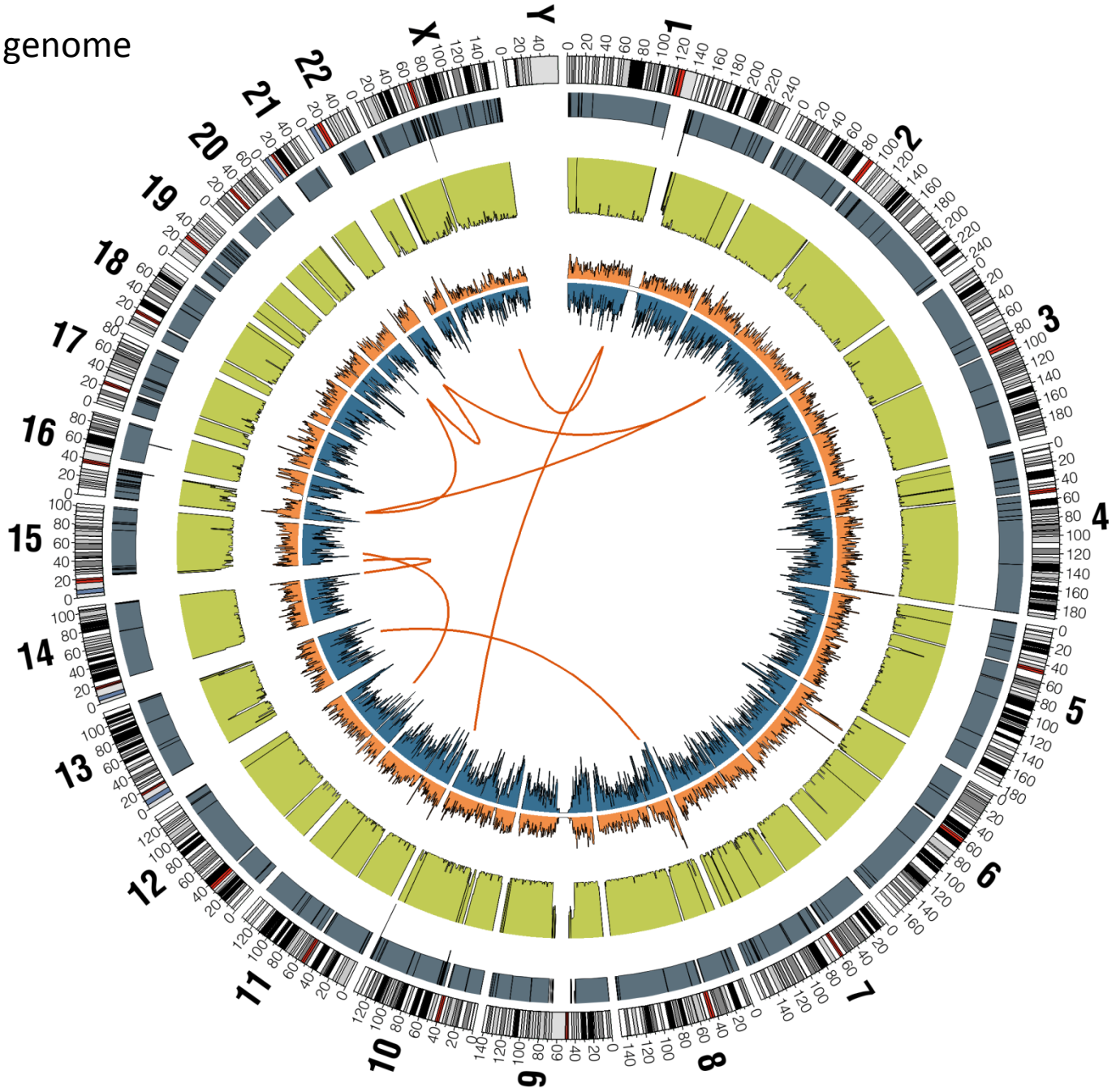
breast cancer genome

PALB2
Frame shift mutation



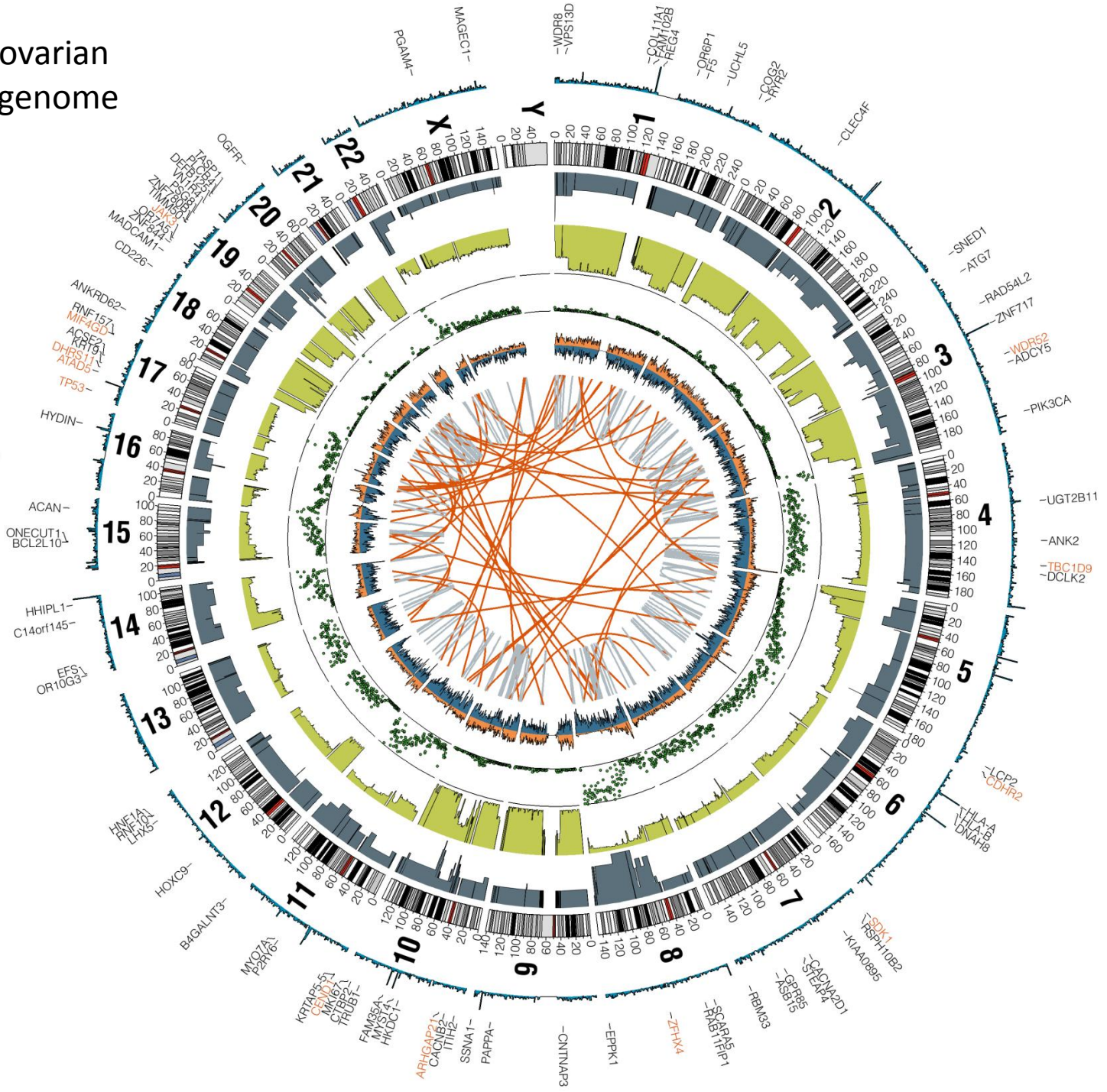
# Germline genome

Complex SV disrupting PALB2 in germline



# Serous ovarian cancer genome

LOH of PALB2 and germline SV retained



Kauff, Offit, *NEJM* 2002; 23;346(21):1609-1534

Robson and Offit, *NEJM.* 2007;357(2):154-62.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

# Management of an Inherited Predisposition to Breast Cancer

Mark Robson, M.D., and Kenneth Offit, M.D., M.P.H.

Positive *BRCA1* or *BRCA2* test result

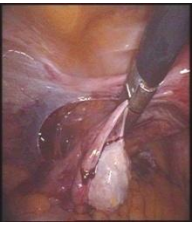
Identify at-risk adult relatives; offer genetic counseling/testing

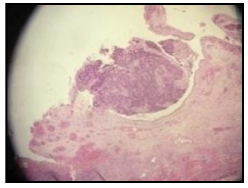
Surgery

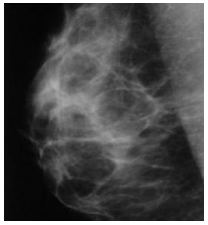
Increased surveillance

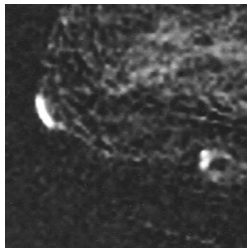
Chemo-prevention

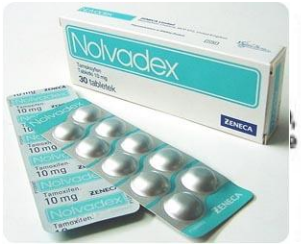
Treatment PARPi

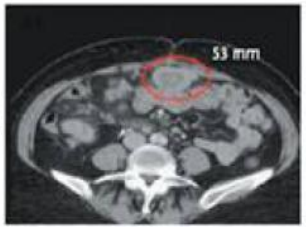


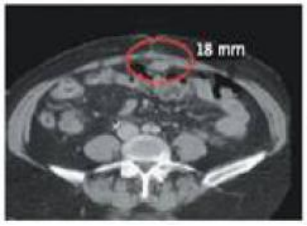




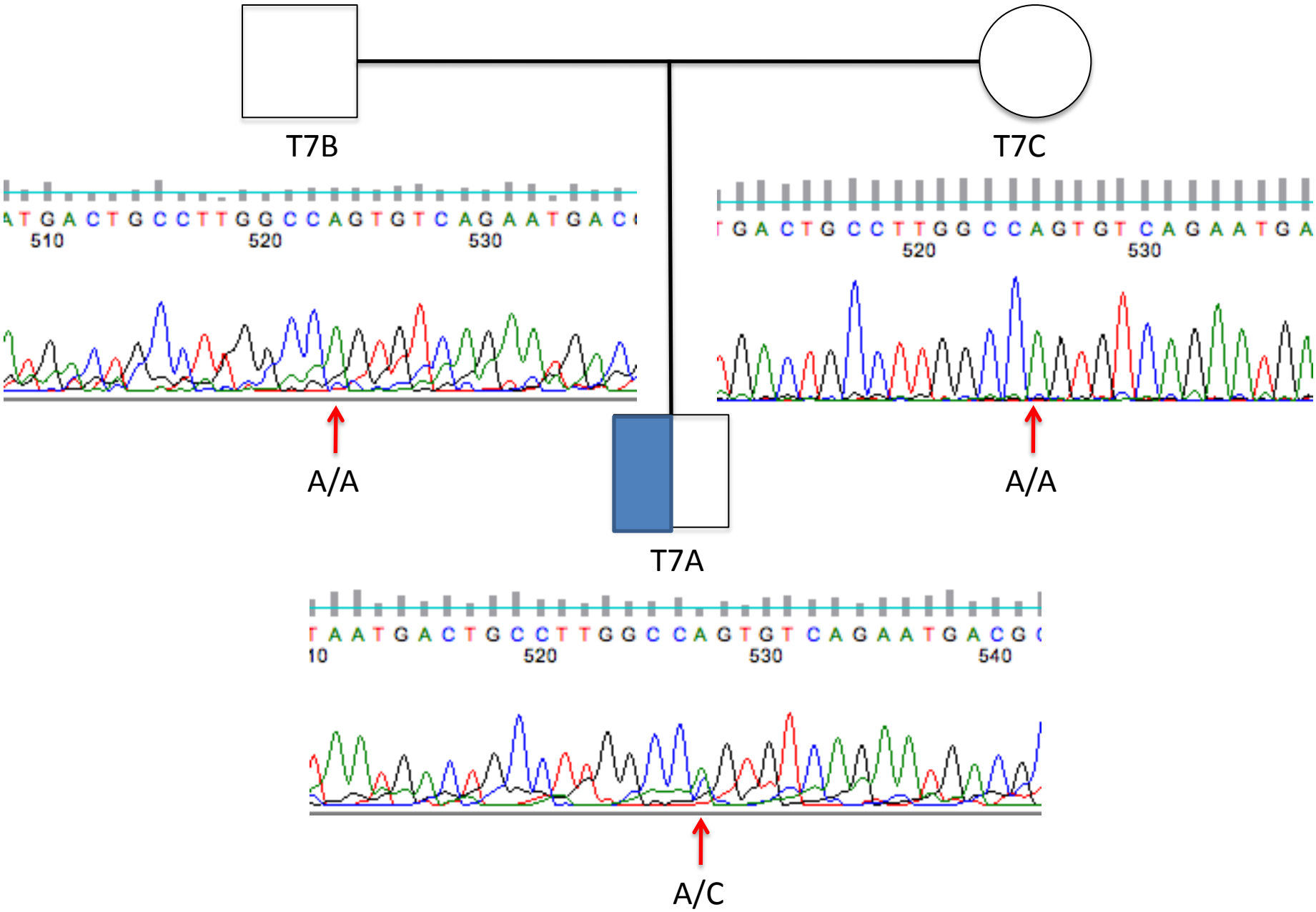




# De Novo Mechanisms in Human Cancer Etiology




Stadler et al. Am J Hum Genet (2012, in press)

# Adapted Berg model

| Return of results | OPT-OUT: | OPT-IN: | | | OPT-IN: | UNAVAILABLE |
|---|---|---|---|---|---|---|
| | RESULTS CHANGE MEDICAL MANAGEMENT | IT MAY BE IMPORTANT INFORMATION BUT IT WILL NOT CHANGE MEDICAL MANAGEMENT | | | PRENATAL TESTING MAY BE AVAILABLE | UNINTERPRETABLE INFORMATION |
| BINs | 1 | 2A | 2B | 2C | 3 | 4 |
| level of risk: | High | Low | Medium | High | Low to person, potentially high to offspring | |
| Examples: | *a single gene change that gives a >60% life time risk for breast cancer OR a single gene change that causes people with it to have less side effects when a certain drug is given* | *gene changes that may slightly alter your risk of common diseases* | *gene changes that may slightly alter your risk of important diseases or single gene conditions for which no firm clinical recommendations exist* | *a single gene change that gives a high life time risk for untreatable neurodegenerative disease* | *Carrier status for severe AR or X-linked disease : childhood onset neurodegenerative disease OR Mental retardation* | *Will need further research before clinical relevance can be established* |

**table adapted from Berg et al. (reproductive bin 3 added)**

# Results of a single genome (exome)

No bin 1 variants

Bin 2a: 3 SNPs

1 = PharmG

*CYP2C9* rs1799853

2 = low risk cancer SNPs

*IL23R* rs11209026

*CLPTM1L* rs402710

Bin 2b: 14 previously reported variants, no novel

3 carrier conditions: Sitosterolemia, Methylmalonic aciduria, Hemansky Pudlak syndrome

# The effect sizes of most GWAS cancer risk SNPS are small and of no clinical utility (Stadler et al 2010,2011; **EGAPP**)




*Exception; modifying SNPs in BRCA2/1 background*

*•Gaudet PLOS Genet, Couch Nat Genet, 2010, submitted*

# HMZ nonsense

| | A | B | C | D | E | F | G | H | I | J | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | GENE | SAMPLE | CHROM | POS | REF | ALT | FILTER | QUAL | ID | SNPEFF_EFFECT | SNPEFF_FUNC | SNPEFF_IM |
| 15275 | OVGP1 | s_11_7_19 | chr1 | 111968121 | C | T | PASS | 3681.66 | rs1264887 | STOP_GAINED | NONSENSE | HIGH |
| 15384 | OR52N4 | s_11_7_19 | chr11 | 5776484 | A | T | PASS | 8847.87 | rs4910844 | STOP_GAINED | NONSENSE | HIGH |
| 15846 | MUC19 | s_11_7_19 | chr12 | 40834955 | C | A | PASS | 3196.79 | rs1078461 | STOP_GAINED | NONSENSE | HIGH |
| 16258 | FAM187B | s_11_7_19 | chr19 | 35719020 | C | T | PASS | 2985.7 | rs541169 | STOP_GAINED | NONSENSE | HIGH |
| 16697 | ADAMTS1 | s_11_7_19 | chr21 | 28216066 | C | T | PASS | 1329.42 | rs370850 | STOP_GAINED | NONSENSE | HIGH |
| 16959 | H2BFM | s_11_7_19 | chrX | 103294760 | C | T | PASS | 558.3 | rs2301384 | STOP_GAINED | NONSENSE | HIGH |

Science AAAS

**A Systematic Survey of Loss-of-Function Variants in Human Protein-Coding Genes**

Daniel G. MacArthur *et al.*
*Science* **335**, 823 (2012);
DOI: 10.1126/science.1215040

Genome-sequencing studies indicate that all humans carry many genetic variants predicted to cause loss of function (LoF) of protein-coding genes, suggesting unexpected redundancy in the human genome. Here we apply stringent filters to 2951 putative LoF variants obtained from 185 human genomes to determine their true prevalence and properties. We estimate that human genomes typically contain ~100 genuine LoF variants with ~20 genes completely inactivated. We identify rare and likely deleterious LoF alleles, including 26 known and 21 predicted severe disease–causing variants, as well as common LoF variants in nonessential genes. We describe functional and evolutionary differences between LoF-tolerant and recessive disease genes and a method for using these differences to prioritize candidate genes found in clinical sequencing studies.

# Cancer Clinical Scenario Conclusions

- Model 1 (targeted mutation testing):
  - Targeted therapy is current practice, but access an issue
  - More expensive with more targets *and more resistance*
  - A resistance genotype may be seen in the germline
  - Cost of companion diagnostics may be impacted by *Prometheus* case (*)
- Model 2 (NGS for disease and actionable variants):
  - Exon capture and whole exome analysis of tumors require germline controls: disclosure of actionable variants in cancer will impact pharmacogenomics as well as non-cancer disease risk in future generations
- Model 3 (NGS + incidentaloma with no threshold):
  - Whole exome/genome analysis of tumors may reveal germline changes with therapeutic as well familial risk implications.
  - May be prefigured if ID HHS-OPHS-2011-0005 change in 45 CFR (*)
  - As in other scenarios, full disclosure of "incidentalome" – outside context of medical practice standards -- will likely lead to clinical and economic inefficiencies (variants, utility concerns).


The end of the beginning