

Ağ Hesaplamasına Dayalı Biyolojik Veriler Işığında Karmaşık Kökenli Hastalıklarının Nedenbilimi

Uğur Sezerman
Acıbadem Üniversitesi

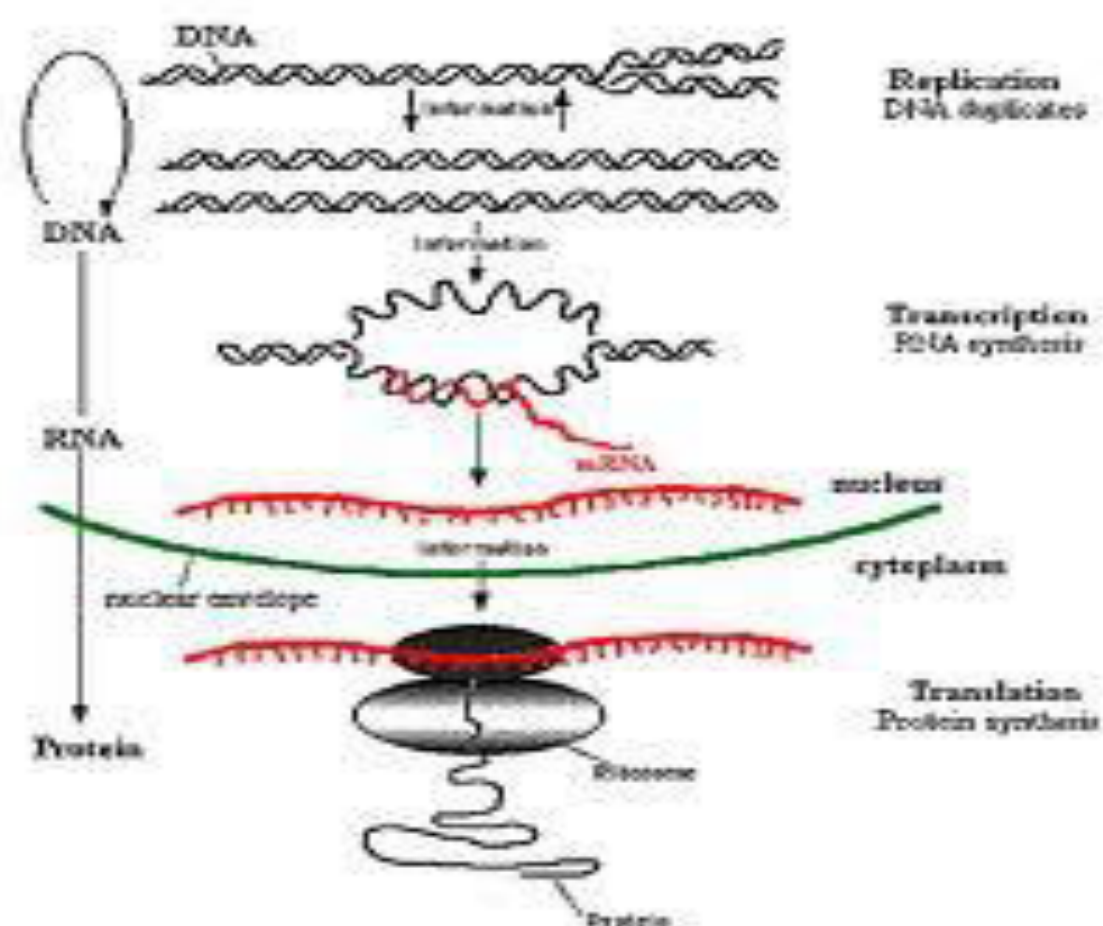


Goals:

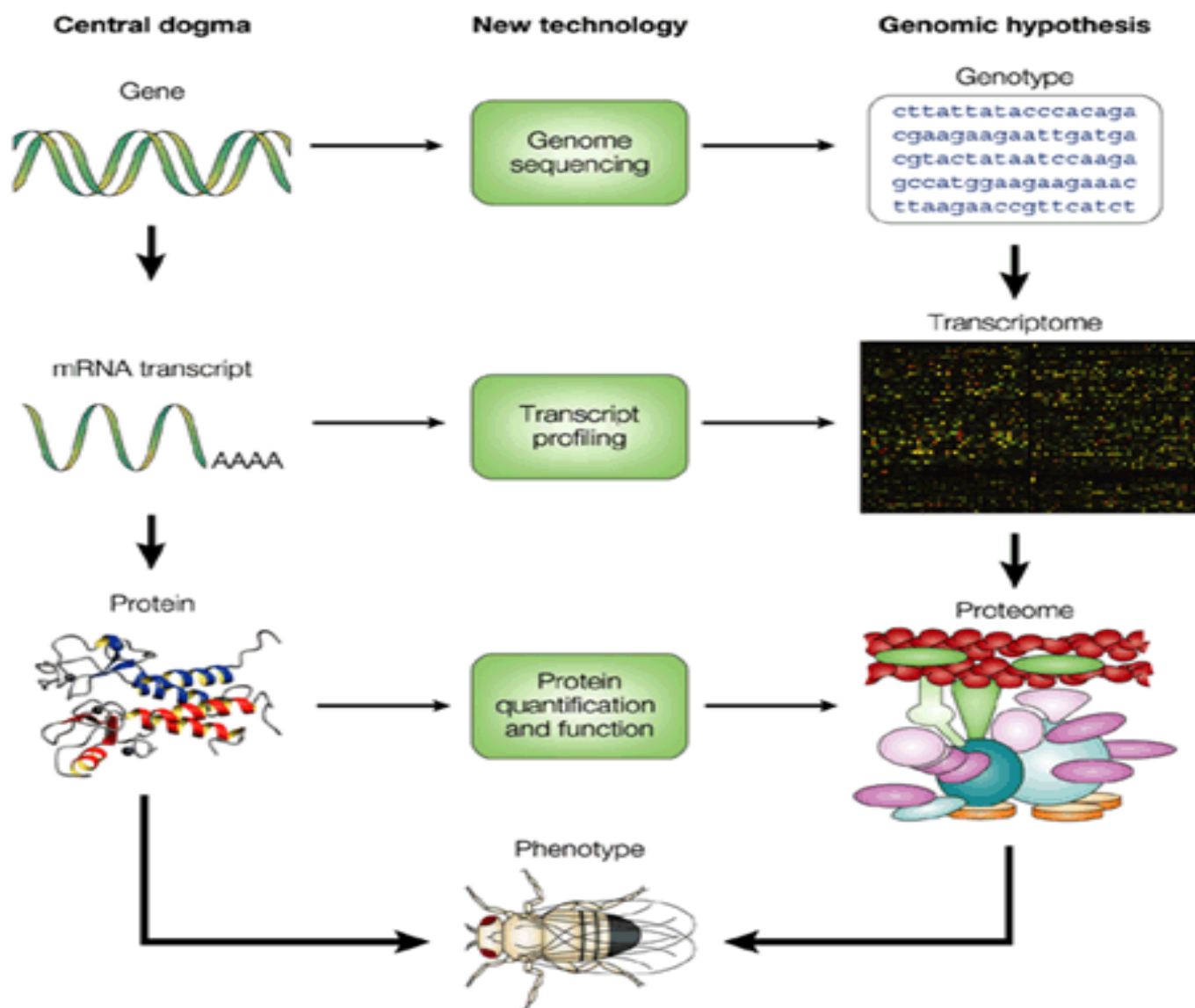
- identify all the approximate 30,000 genes in human DNA,
- determine the sequences of the 3 billion chemical base pairs that make up human DNA,
- store this information in databases,
- improve tools for data analysis,
- transfer related technologies to the private sector, and
- address the ethical, legal, and social issues (ELSI) that may arise from the project.

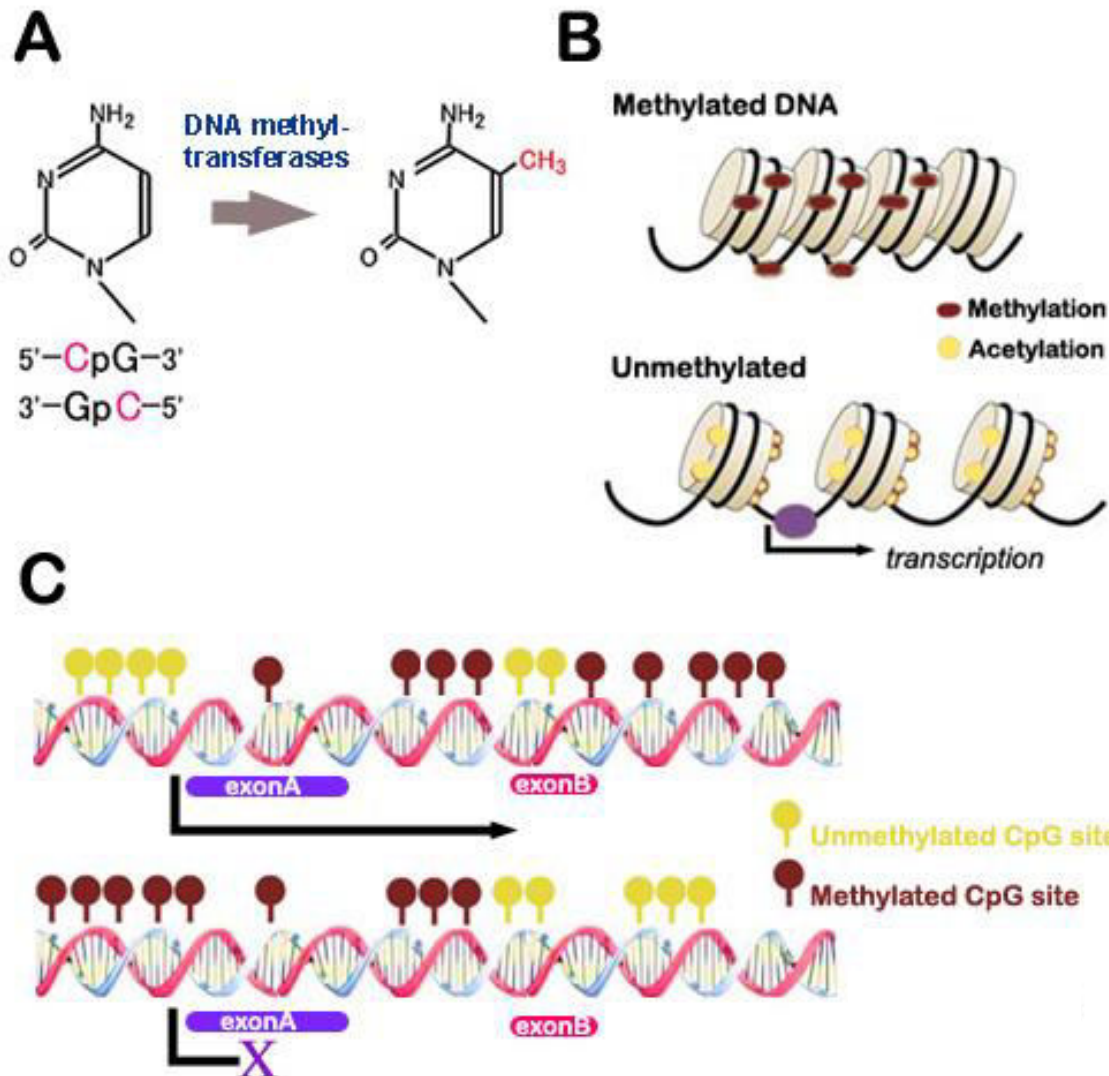
Milestones:

- 1990: Project initiated as joint effort of U.S. Department of Energy and the National Institutes of Health
- June 2000: Completion of a working draft of the entire human genome (covers >90% of the genome to a depth of 3-4x redundant sequence)
- February 2001: Analyses of the working draft are published
- April 2003: HGP sequencing is completed and Project is declared finished two years ahead of schedule



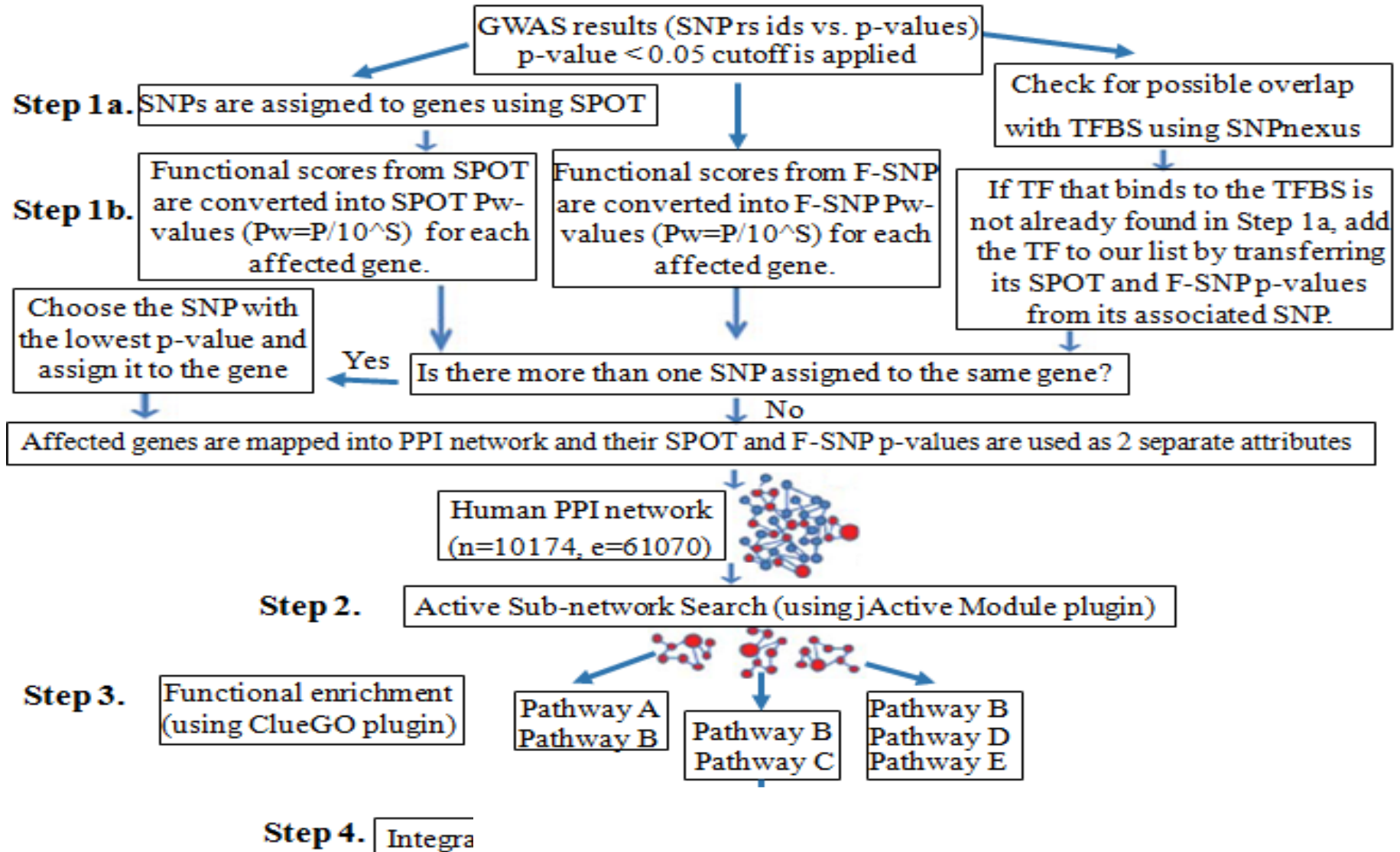
The Central Dogma of Molecular Biology





Hypomethylation
Hypermethylation

Our Methodology (PANOGA)



Partial Epilepsy Dataset

# of Cases	# of Controls	# of genotyped SNPs	Platform
3,445	6,935	528,745 SNPs	Illumina, Human610-Quadv1 genotyping chips

Table 5. Summary of Partial Epilepsy (PE) dataset ([Kasperaviciute, et al., 2010](#)).

- 1429 patients with epilepsies of unknown cause (classified as “cryptogenic”), 919 cases with mesial temporal lobe epilepsy with hippocampal sclerosis, 241 with cortical malformations and 222 patients with various tumors, other smaller subgroups such as trauma, stroke, perinatal insults, infections, etc.
- Cochran–Mantel–Haenszel test results were used as the genotypic p-values of the identified SNPs.
- Using $P < 0.05$ cutoff:
 - 28,450 SNPs were included.

KEGG Term	p values	SNPs in GWAS	SNP Targeted Genes	Previous Studies Showing Support	Wang et al. Study	OMIM	GWAS on PE	CNV Study on Epilepsy	Epi GAD	Rogic et al. Study
Complement and coagulation cascades	2,16E-25	34	12	(Aronica, et al., 2008 ; Okamoto, et al., 2010)	-	Y	-	-	-	Y
Cell cycle	1,03E-24	24	14	(Aronica, et al., 2008 ; Jimenez-Mateos, et al., 2008 ; Limviphuvadh, et al., 2010)	-	Y	-	-	-	Y
Focal adhesion	7,10E-23	97	20	(Brockschmidt, et al., 2012)	Y	Y	Y	-	-	Y
ECM-receptor interaction	1,62E-22	62	14	(Aronica, et al., 2008)	Y	Y	-	-	-	Y
Jak-STAT signaling pathway	1,16E-21	24	16	(Jimenez-Mateos, et al., 2008 ; Okamoto, et al., 2010)	Y	Y	-	-	-	Y
MAPK signaling pathway	2,32E-19	73	23	(Jimenez-Mateos, et al., 2008 ; Okamoto, et al., 2010 ; Zhou, et al., 2011)	Y	Y	Y	-	Y	Y
Proteasome	1,15E-18	11	4	(Lauren, et al., 2010)	-	-	-	-	-	-
Ribosome	1,57E-18	2	2	(Lauren, et al., 2010)	-	-	-	-	-	Y
Calcium signaling pathway	5,73E-18	154	22	(Jimenez-Mateos, et al., 2008 ; Limviphuvadh, et al., 2010 ; Okamoto, et al., 2010 ; Zhou, et al., 2011)	Y	Y	Y	Y	Y	Y
Regulation of actin cytoskeleton	9,23E-18	88	19		Y	Y	-	Y	-	Y
Adherens junction	1,01E-17	79	13		-	-	Y	-	-	Y
Pathways in cancer	3,94E-17	112	22		Y	Y	Y	-	-	Y
Gap junction	6,32E-17	147	18	(Lauren, et al., 2010)	Y	Y	Y	-	-	Y
Apoptosis	3,72E-16	37	13	(Jimenez-Mateos, et al., 2008)	Y	Y	-	-	-	Y
Long-term depression	2,90E-15	151	15	(Lauren, et al., 2010)	Y	Y	Y	Y	Y	Y
Axon guidance	4,01E-15	59	12	(Jimenez-Mateos, et al., 2008 ; Limviphuvadh, et al., 2010)	-	-	-	-	-	Y
Fc gamma R-mediated phagocytosis	2,22E-14	66	12		Y	Y	Y	Y	-	Y
Tight junction	2,82E-14	82	13		Y	Y	Y	-	-	Y
ErbB signaling pathway	4,04E-14	86	12		Y	Y	Y	-	-	Y
Wnt signaling pathway	6,28E-14	44	13	(Aronica, et al., 2008 ; Okamoto, et al., 2010)	Y	Y	Y	-	-	Y

Table 6. Comparison of the top 20 SNP-targeted pathways with the pathways of the known genes, as associated to partial epilepsy.

Intracranial Aneurysm Dataset

Population	# of Cases	# of Controls	# of genotyped SNPs	Platform
European	2,780	12,515	832,000	Illumina
Japanese	1,069	904	312,712	Illumina,

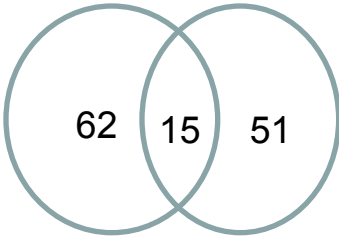
Table 7. Summary of Intracranial Aneurysm (IA)dataset.

- In both datasets, each SNP's genotypic p-value of association is calculated via Cochran-Armitage trend test.
- Using $P < 0.05$ cutoff:
 - 44,351 SNPs were included for EU population,
 - 14,034 SNPs were included for JP population.

	P-values		Rank		# of Associated SNPs in GWAS		# of Common SNPs in GWAS	# of SNP Targeted Genes (STGs)		# of Common STGs	% Common Genes in Both Populations		Common SNPs in GWAS
KEGG Term	EU	JP	EU	JP	EU	JP		EU	JP		EU	JP	
MAPK signaling pathway *	3.53E-27	2.70E-18	1	8	133	43	1	14	18	2	14.29	11.11	rs791062

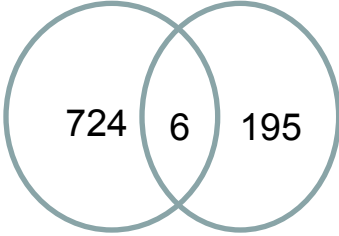
of SNP Targeted Genes in Top 10 Pathways

EU population JP population



of SNPs from GWAS in Top 10 Pathways

EU population JP population



5	18	1	11	10	2	18.18	20	rs744910
6	20	3	15	9	5	33.33	55.56	rs2053423. rs1440375. rs744910
0	15	0	6	4	0	0	0	
7	45	1	21	14	5	23.81	35.71	rs4678167
2	1	0	6	1	0	0	0	
5	34	1	13	11	2	15.38	18.18	rs1561798
5	13	0	8	4	1	12.5	25	
2	36	1	18	14	1	5.556	7.143	rs4678167
8	14	0	7	7	1	14.29	14.29	

for both populations in IA. 7 out of the top 10 pathways are related diseases in KEGG Disease Pathways Database.

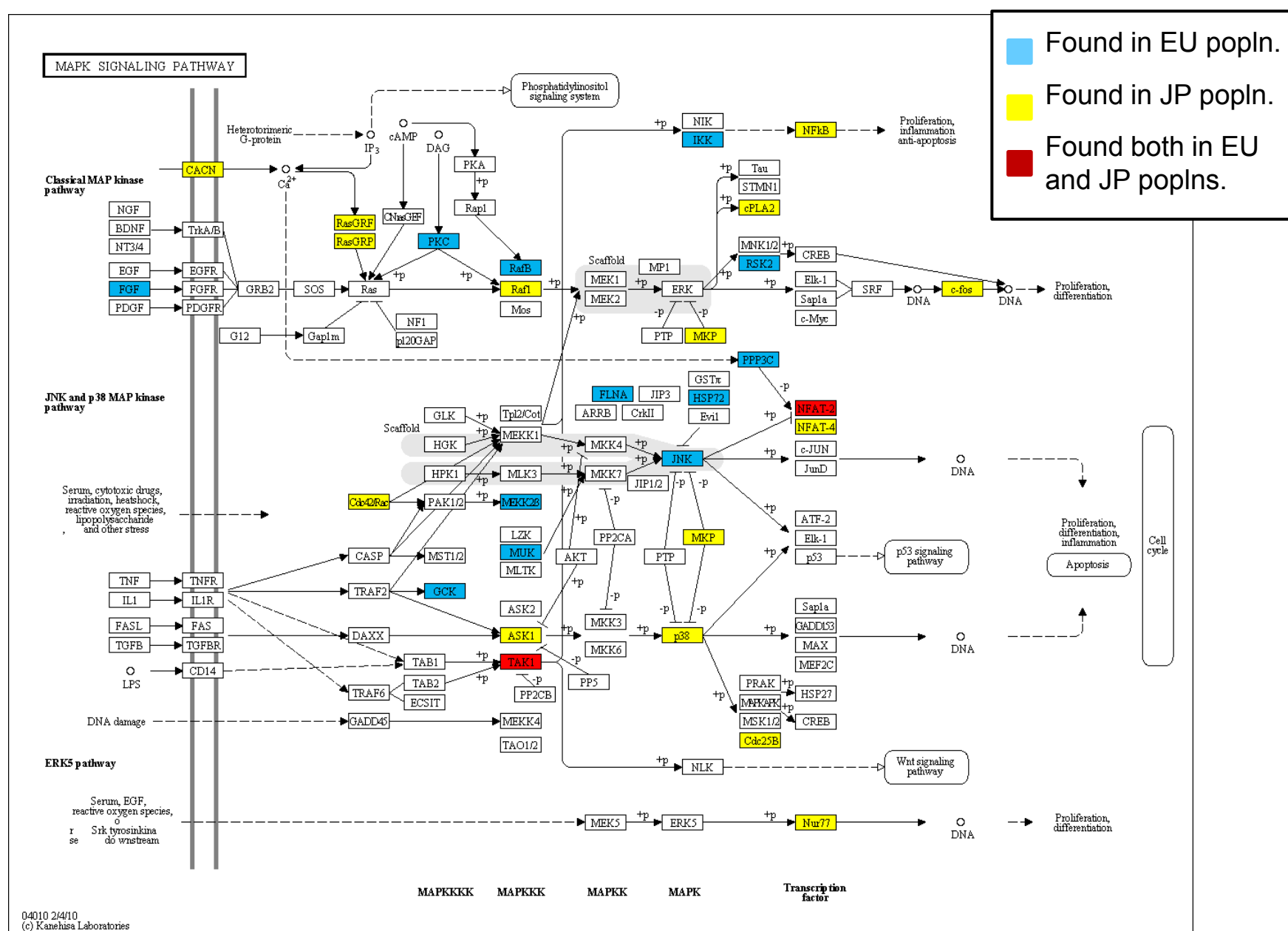


Figure 17. KEGG pathway map for MAPK signaling pathway. The set of genes shown in blue includes genes that are found for EU dataset; yellow includes genes that are found for JP dataset; red includes genes that are found both by EU and JP GWAS of IA.

Behcet's disease dataset

Population	# of Cases	# of Controls	# of genotyped SNPs	Platform
Turkish	1,215	1,278	311,459	Illumina, Infinium assay
Japanese	612	740	500,568	Affymetrix Gene Chip Human Mapping 500K

Table 10. Summary of Behcet's disease dataset.

- In both datasets, each SNP's genotypic p-value of association is calculated via calculated via allelic chi-squared test.
- Using $P < 0.05$ cutoff:
 - 18,479 SNPs were included for TR population,
 - 20,594 SNPs were included for JP population.

Common pathways in Turkish and Japanese Populations

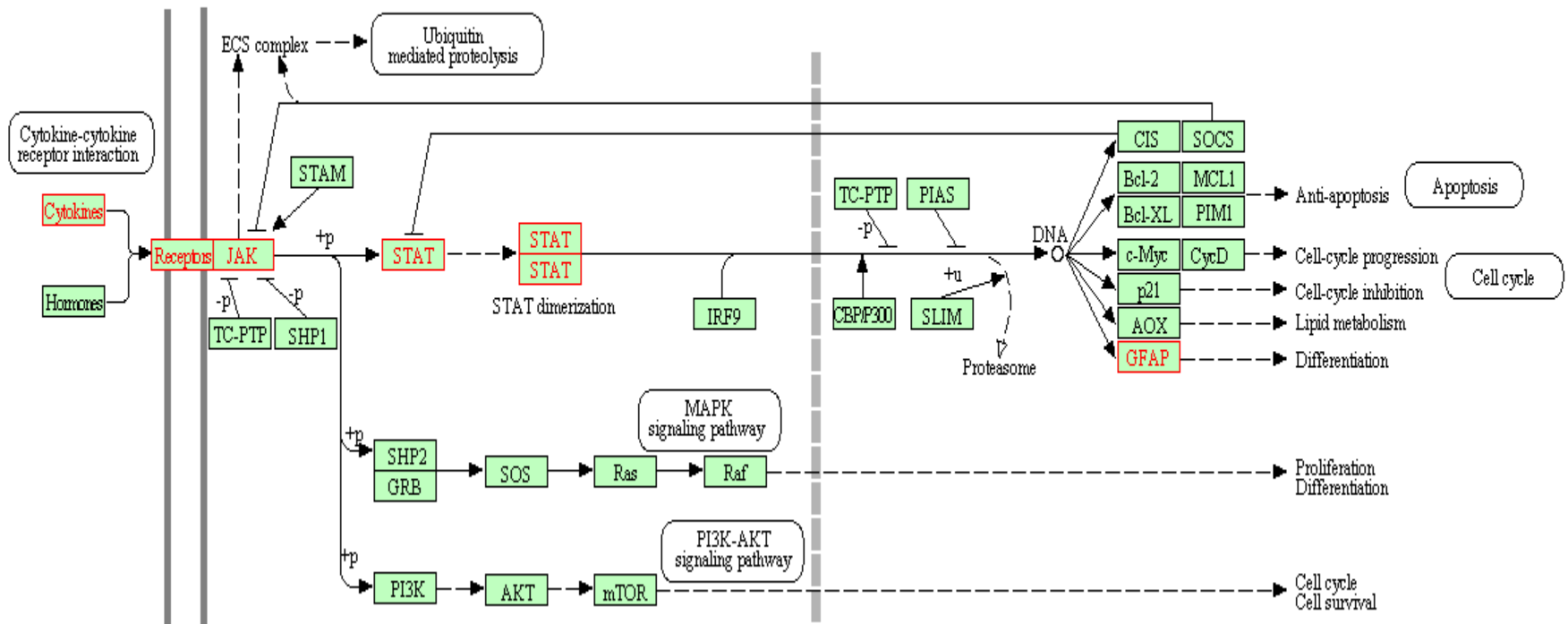
Antigen processing and presentation
Adipocytokine signaling pathway
Aldosterone-regulated sodium reabsorption
Amoebiasis
AMPK signaling pathway
Axon guidance
cAMP signaling pathway
cGMP-PKG signaling pathway
Circadian rhythm
ErbB signaling pathway
Fc gamma R-mediated phagocytosis
Herpes simplex infection
Inflammatory mediator regulation of TRP channels

Jak-STAT signaling pathway
MAPK signaling pathway
Maturity onset diabetes of the young
NOD-like receptor signaling pathway
Notch signaling pathway
PPAR signaling pathway
Prolactin signaling pathway
Rap1 signaling pathway
Ras signaling pathway
Tight junction
Tuberculosis
Wnt signaling pathway

* Common pathways (25) in first 40 pathways of each population

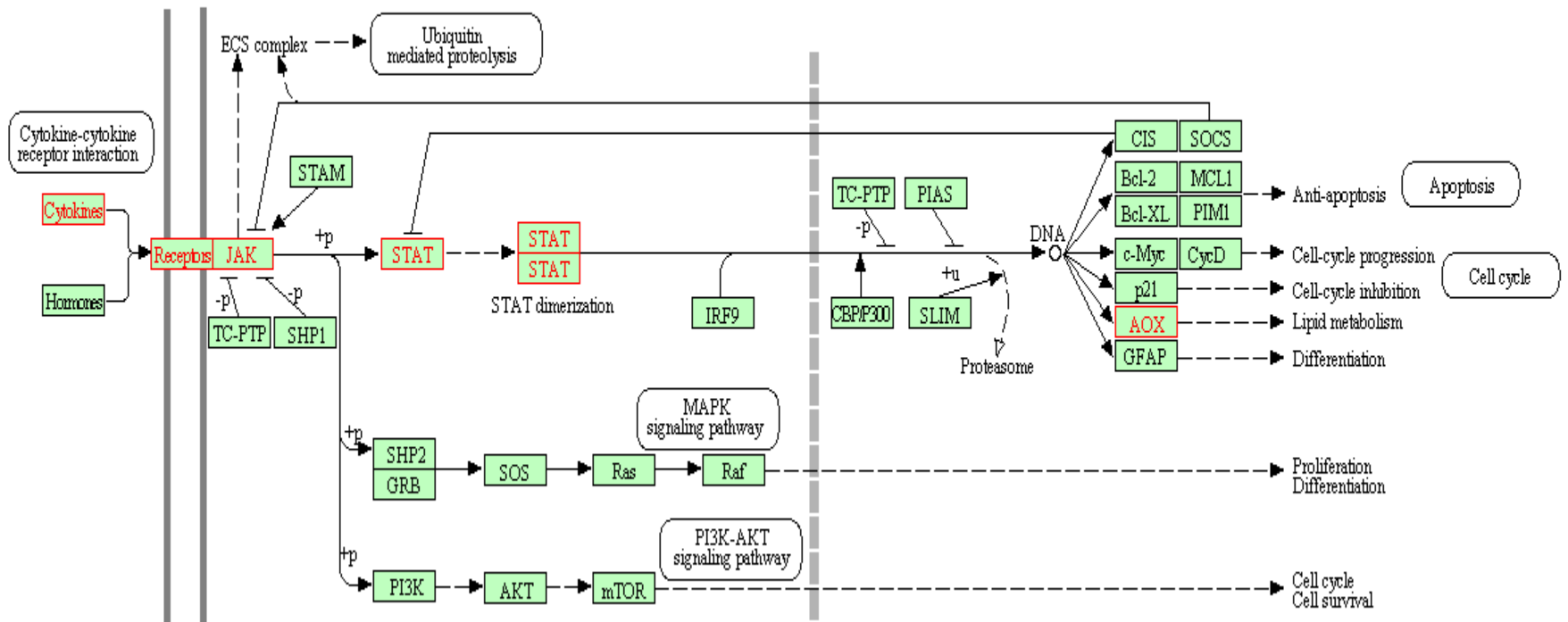
Highest scoring Jak-STAT path in Turkish population

JAK-STAT SIGNALING PATHWAY



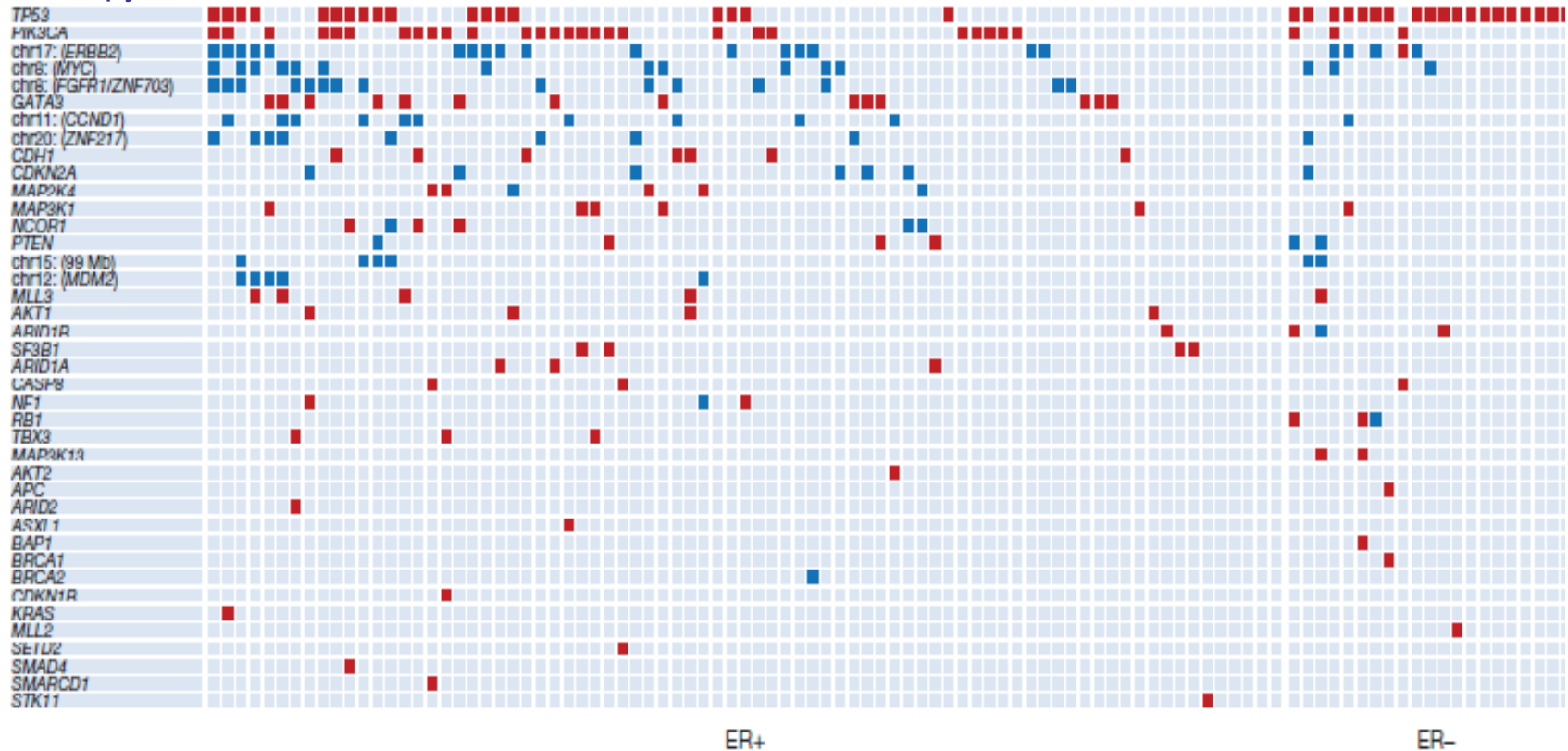
Highest scoring Jak-STAT path in Japanese population

JAK-STAT SIGNALING PATHWAY



Frequent cancers include high number of very rare genomic segments

- Somatic mutation
- Copy Number Variation



(whole genome sequencing breast cancers)

Identification of Cancer drivers

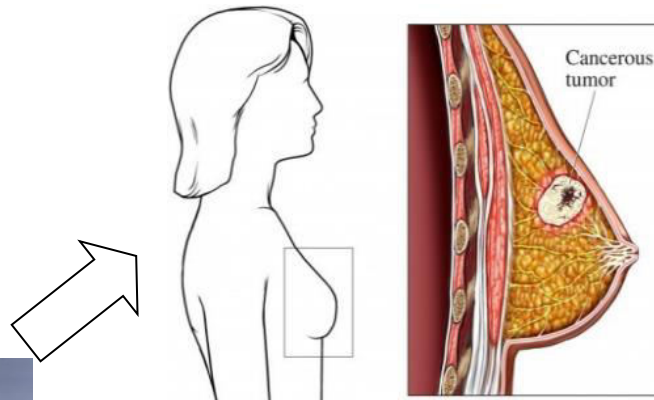
- Identification of individualized driver mechanisms that lead to tumour specific cancer progression can improve patient's outcome
- Goal: Identification of targetable driver mechanism

Precision Medicine

Concept: Identify the targets to be treated in each patient

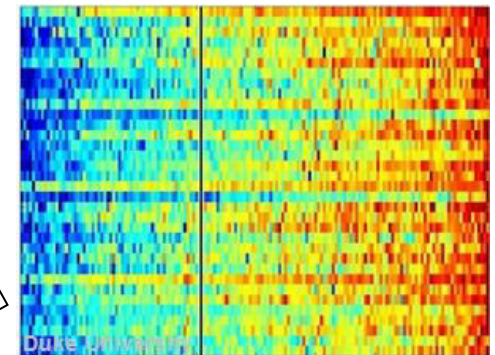
Clinical evidence

Therapy matched to
genomic alteration



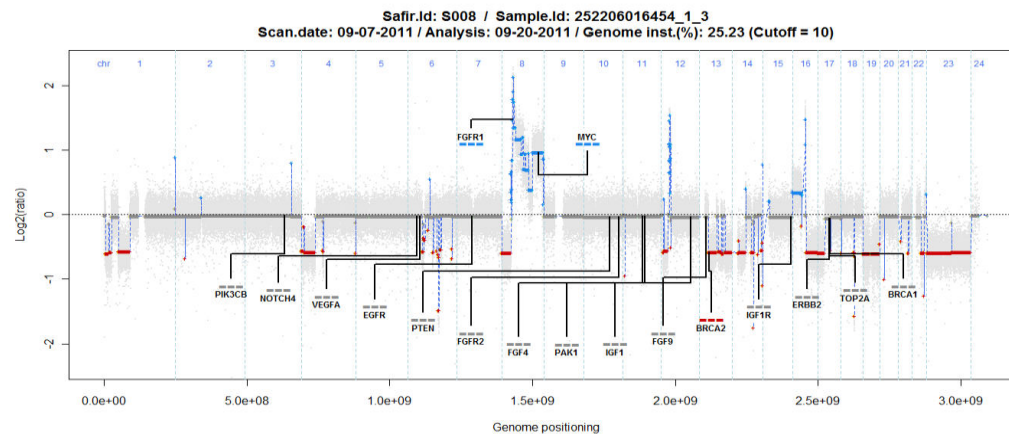
**What is the optimal
Biotechnology ?**

Molecular analysis



**What is the optimal
Algorithm ?**

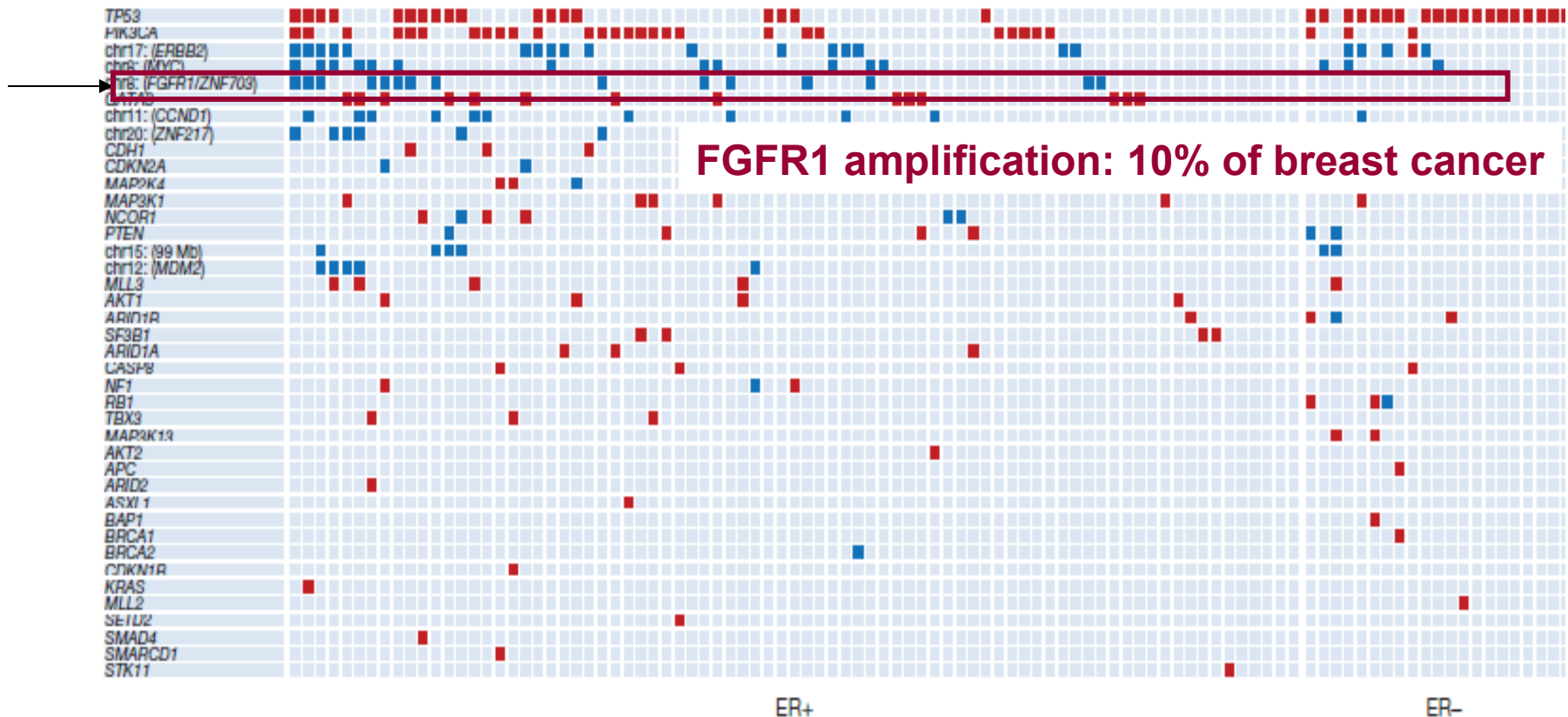
Target identification



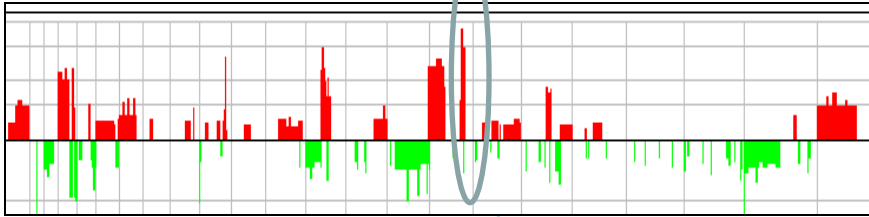
Andre, ESMO, 2012

Stratified medicine

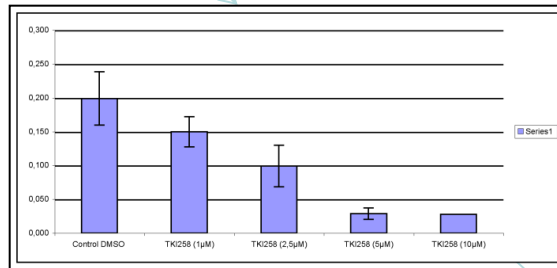
- Drug development or implementation in a strata defined by a molecular alteration



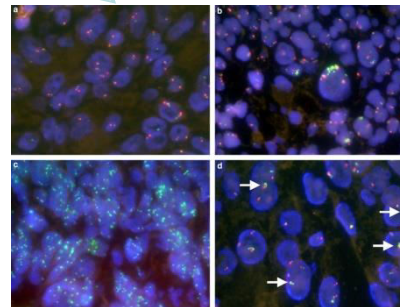
Translational research to feed stratified medicine



FGFR1: amplification in 10% BC

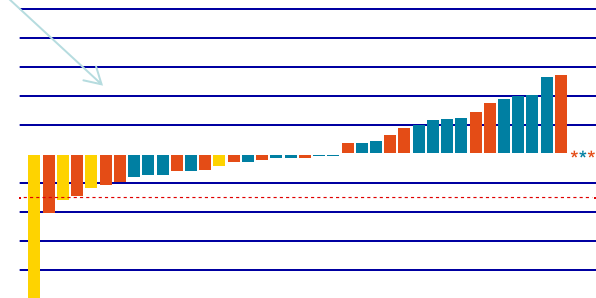


FGFR1 inhibitors present higher sensitivity on FGFR1-amplified CC

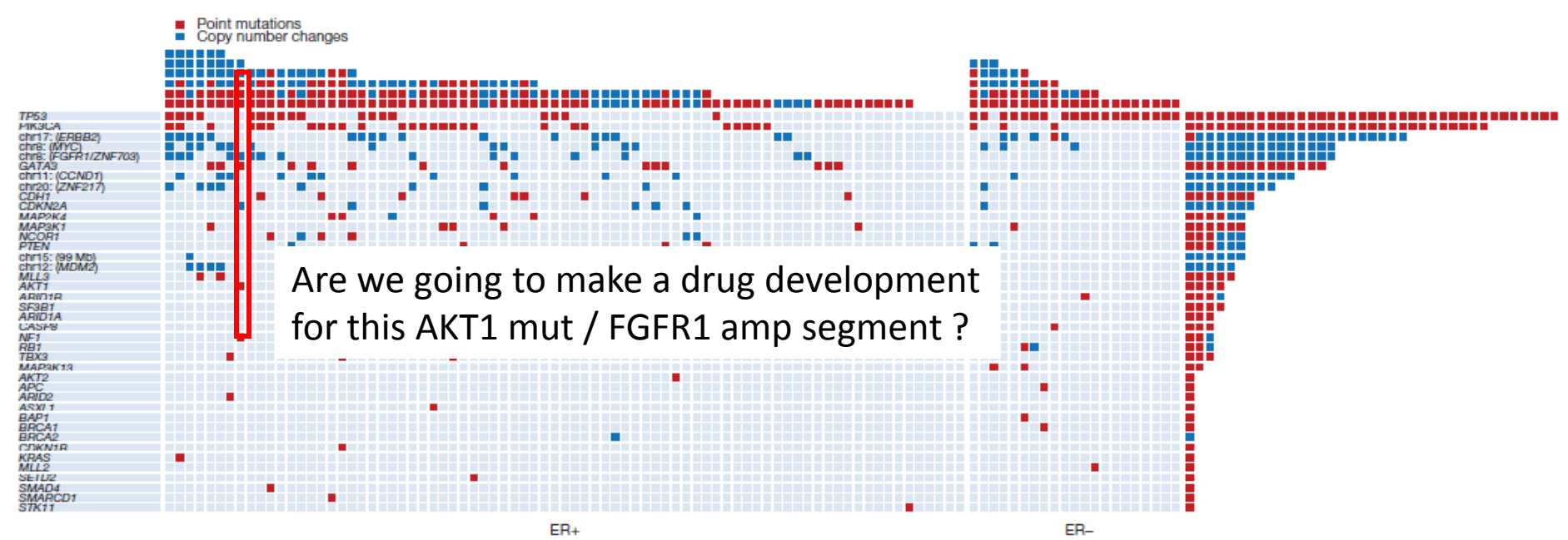


Set-up genomic test (FISH)

Run phase II trial
Testing the FGFR1
Inh in patients with
FGFR1 amp BC

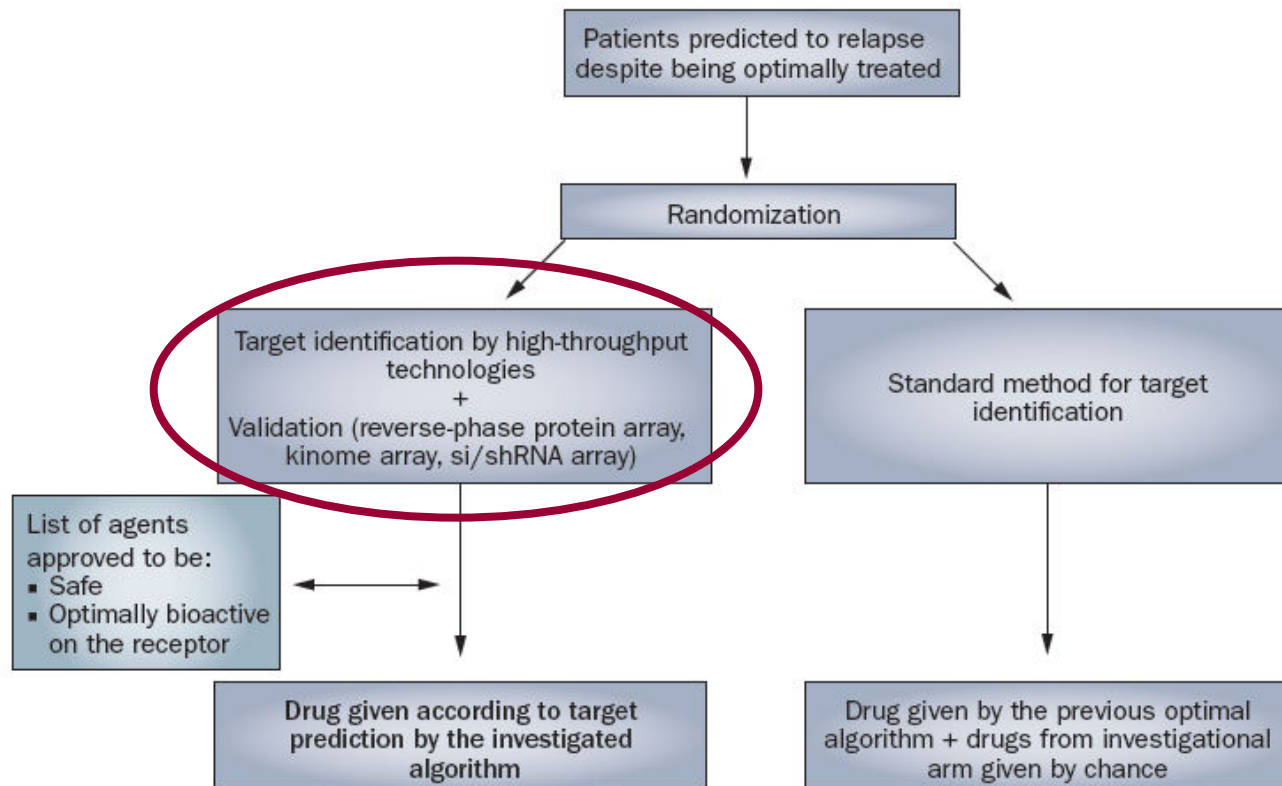


Evolution: GENOMIC DISEASES ARE BECOMING TO RARE OR COMPLEX TO ALLOW DRUG DEVELOPMENT IN GENOMIC SEGMENTS



How to move forward ?

Implications of Personalized Medicine



How to move there ???

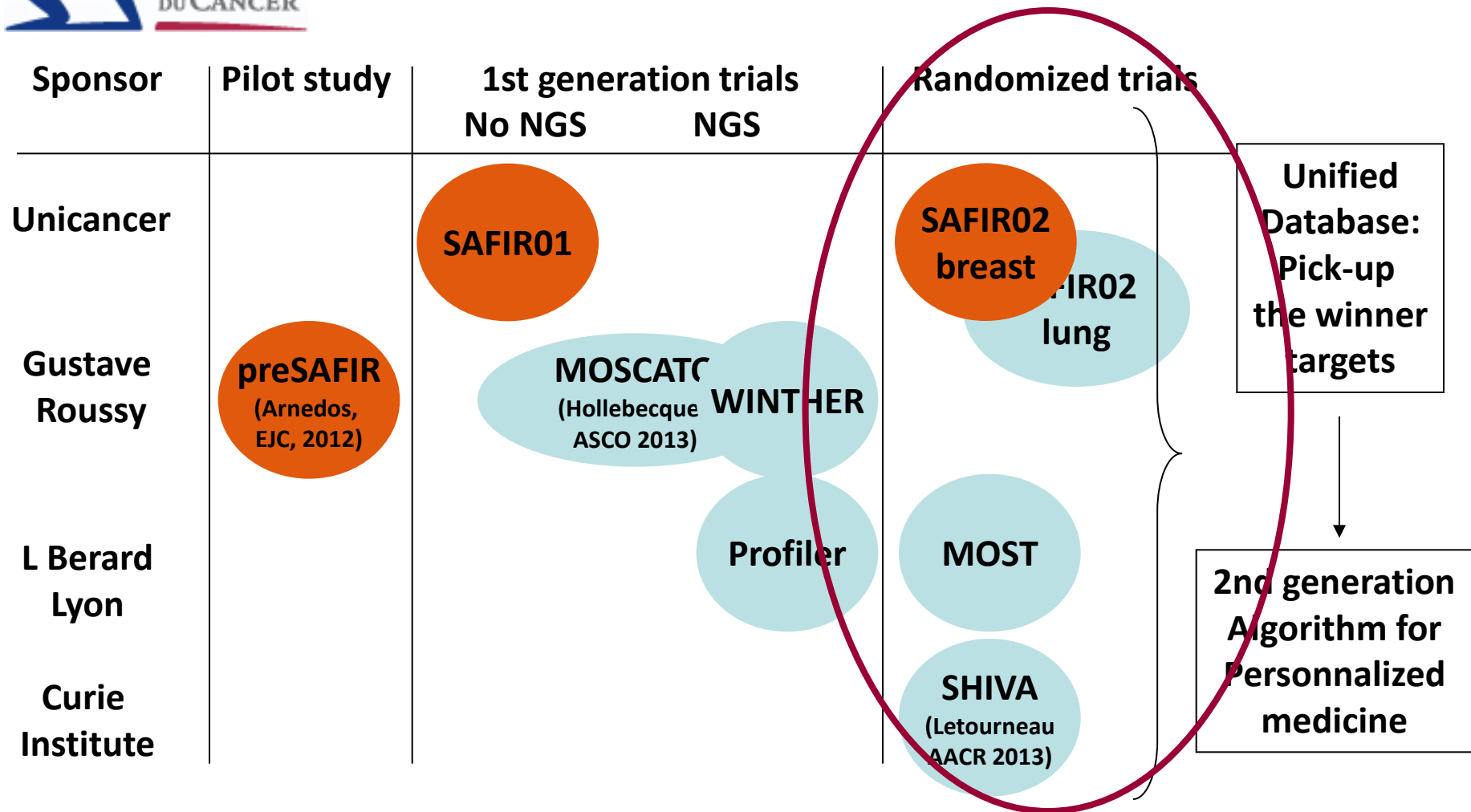
OPINION

Implications of personalized medicine —perspective from a cancer center

Thomas Tursz, Fabrice Andre, Vladimir Lazar, Ludovic Lacroix
and Jean-Charles Soria

Tursz, T. et al. *Nat. Rev. Clin. Oncol.* 8, 177–183 (2011)

Ongoing molecular screening or personalized medicine programs in France



Overall : >2 000 planned patients (all tumor types), >800 already included

Breast Cancer: > 1 000 planned, >70 already treated

Goal: To generate optimal algorithm for individualized therapy

SAFIR01

- 423 patients were included, and biopsy samples were obtained from 407 (metastatic breast cancer was not found in four). CGH array and Sanger sequencing were feasible in 283 (67%) and 297 (70%) patients, respectively.
- A targetable genomic alteration was identified in 195 (46%) patients, most frequently in PIK3CA (74 [25%] of 297 identified genomic alterations), CCND1 (53 [19%]), and FGFR1 (36 [13%]). 117 (39%) of 297 patients with rare genomic alterations (<5% of the general population), including AKT1 mutations, and EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET high-level amplifications.
- Therapy could be personalised in 55 (13%) of 423 patients. Of the 43 patients who were assessable and received targeted therapy, four (9%) had an objective response, and nine others (21%) had stable disease for more than 16 weeks.
- Serious (grade 3 or higher) adverse events related to biopsy were reported in four (1%) of enrolled patients, including pneumothorax (grade 3, one patient), pain (grade 3, one patient), haematoma (grade 3, one patient), and haemorrhagic shock (grade 3, one patient).

A Protocol to Determine Somatic Modifications

- Exome Sequencing of tumour sample and control sample(Blood)
- Identification of somatic alterations in the tumour

Driver mutations

Copy Number Variations (CNV)

SNPs

Ch r	Pos	Ref -> Alt Genome Protein Effect	Gen e	dbSNP	CGC* Tumor Type	DrugBank
2	209113112	C -> T R -> H Missens e	IDH1	rs12191350	Glioblastoma	-
17	7577545	T -> C M -> V Missens e	TP53	rs48335269 rs39751643 7	Glioma	Acetylsalic ylic acid

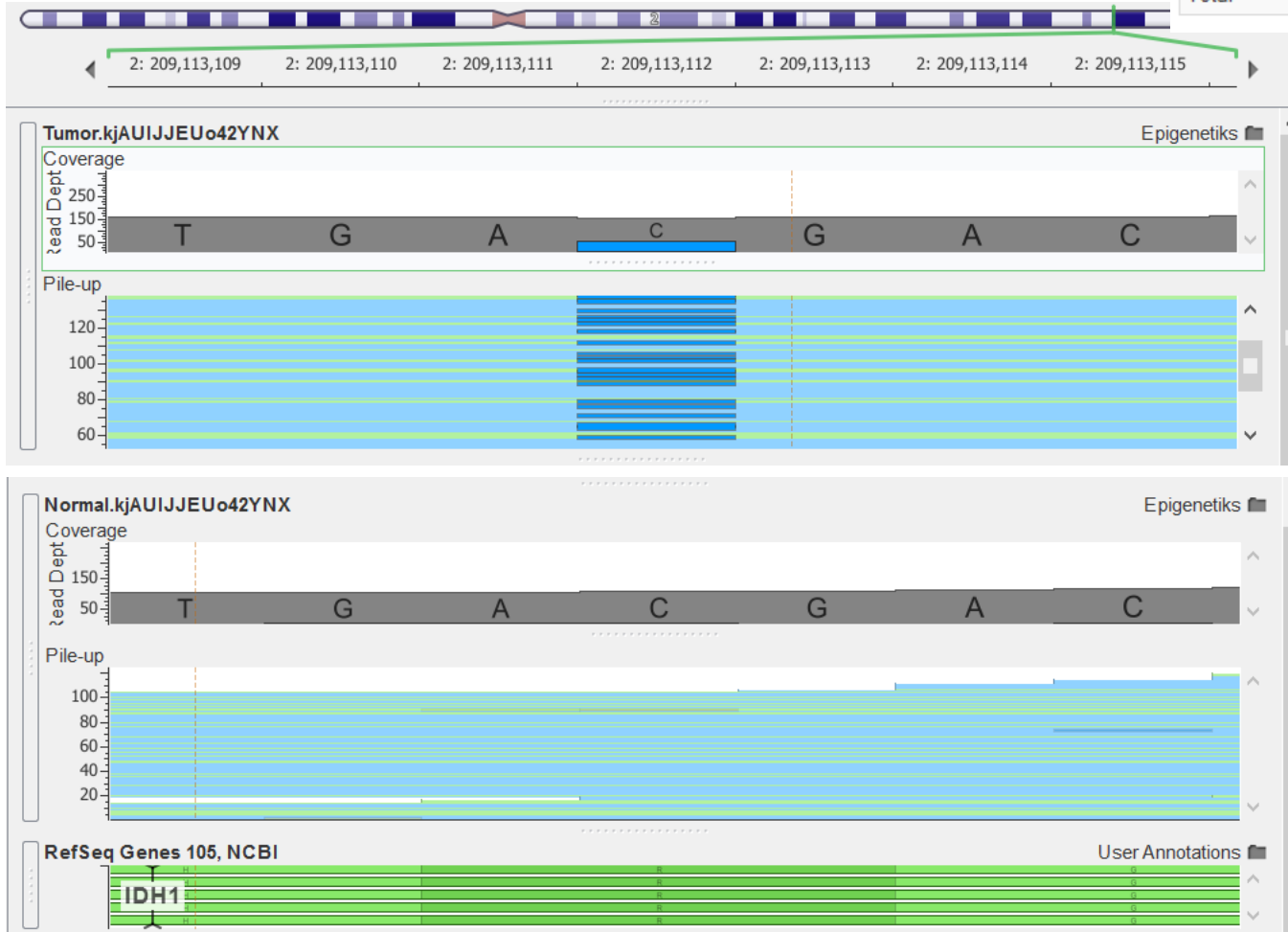
SNPs

Chr	Pos	Ref -> Alt Genome Protein Effect	Gene	dbSNP	CGC* Tumor Type	DrugBank
2	209113112	C -> T R -> H Missense	IDH1	rs12191350	Glioblastoma	-
17	7577545	T -> C M -> V Missense	TP53	rs48335269 rs39751643	Glioma	Acetylsalicylic acid

* Cancer Gene Census

SNPs

Type	Base	Count	% of Total	Mean Quality
(match)	C	99	66.4	30.8
(mismatch)	T	50	33.6	32.3
Total		149	100	31.3



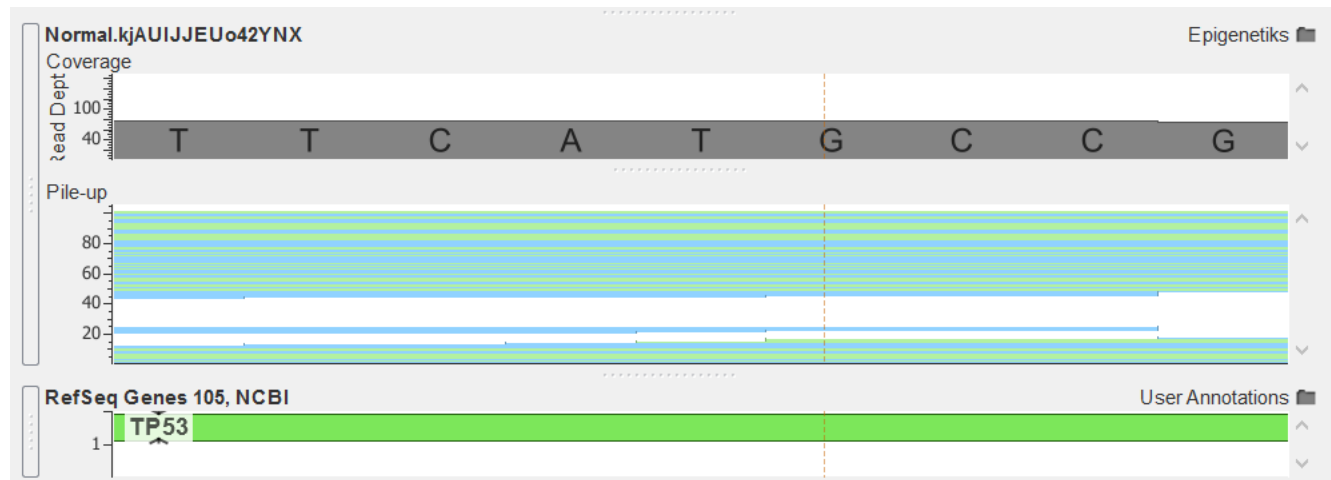
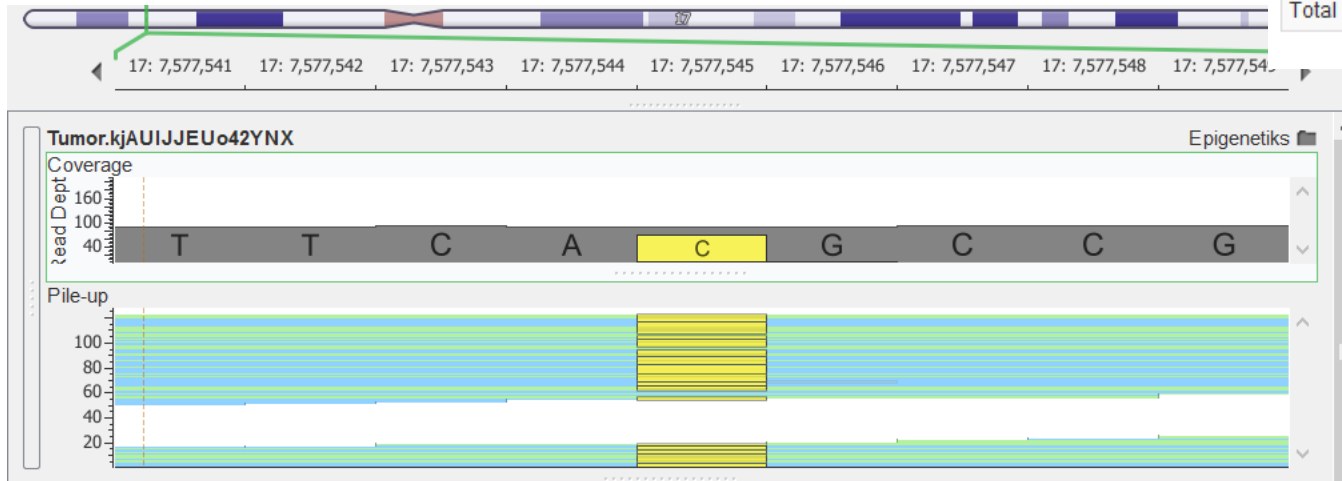
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2	209113112	C -> T R -> H Missense	IDH1	rs12191350	Glioblastoma	-
17	7577545	T -> C M -> V Missense	TP53	rs48335269 5 rs39751643 7	Glioma	Acetylsalicylic acid

* Cancer Gene Census

SNPs

Type	Base	Count	% of Total	Mean Quality
(match)	T	21	24.1	29.7
(mismatch)	C	66	75.9	29.0
Total		87	100	29.1



INDELS

Ch r	Pos	Ref	Al t	Normal GT	Tumo r GT	CGC* Tumor Type	DrugBank
5	6757532 3	ATT	A	0/1	0/1	Glioblastom a	Isoprenaline
17	7579643	CCCCC AGCCC TCCAG GT	C	0/0	0/1	Glioma	Acetylsalicyli cacid

* Cancer Gene Census

INDELS

Ch r	Pos	Ref	Al t	Normal GT	Tumo r	CGC* Tumor Type	DrugBank
5	67575323	ATTT	A	0/1	0/1	Glioblastoma	Isoprenaline
17	7579643	CCCCC AGCCC TCCAG GT	C	0/0	0/1	Glioma	Acetylsalicylic acid

* Cancer Gene Census

INDELS

Ch r	Pos	Ref	Al t	Normal GT	Tumo r GT	CGC* Tumor Type	DrugBank
5	67575323	ATTT	A	0/1	0/1	Glioblastoma	Isoprenaline
17	7579643	CCCCC AGCCC TCCAG GT	C	0/0	0/1	Glioma	Acetylsalicylic acid

* Cancer Gene Census

INDELs



Copy Number Variation

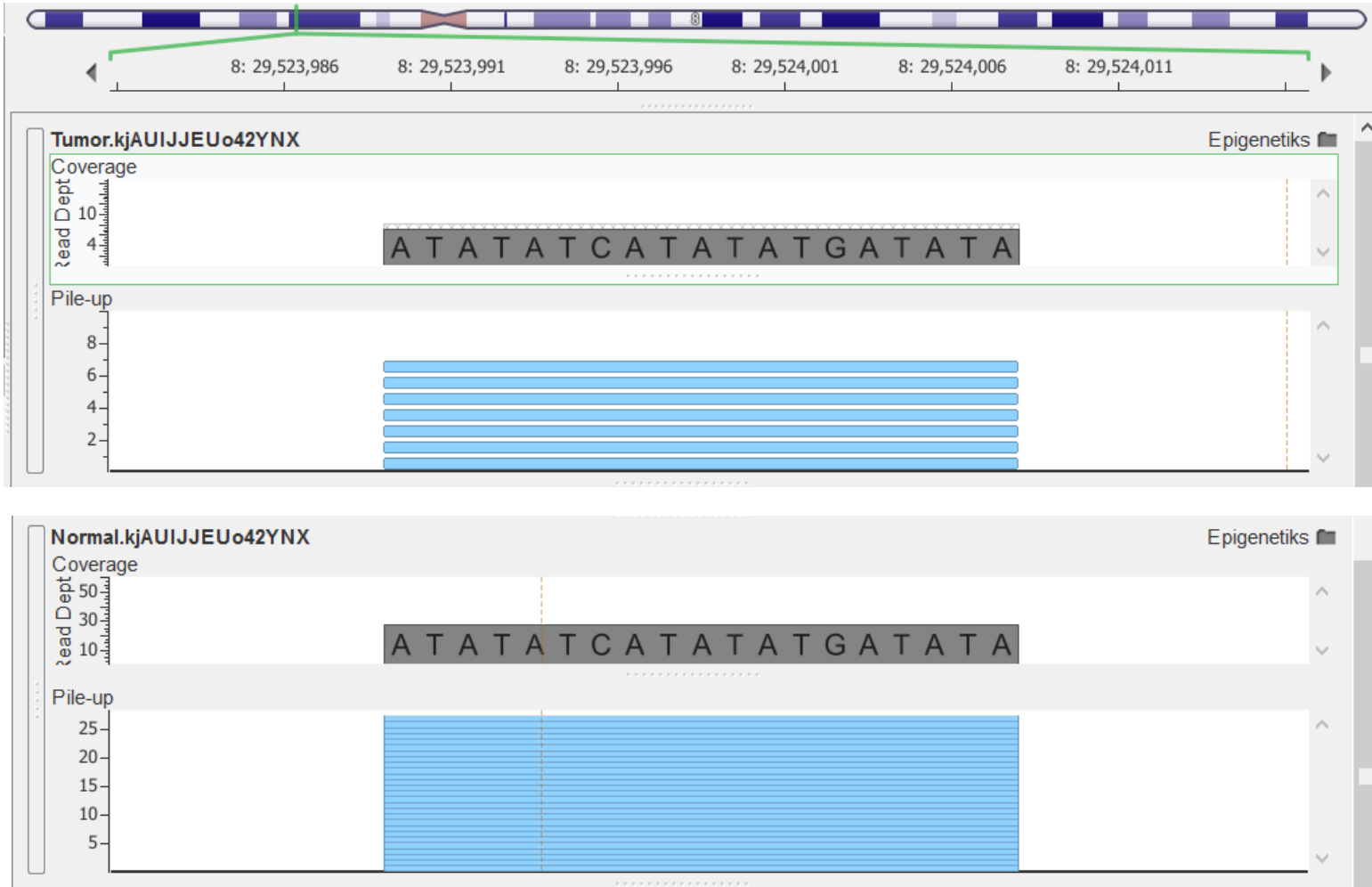
Ch r	Start	End	Normal Depth	Tumor Depth	Log Ratio
8	2952399 0	2952400 7	20.6	4.3	-2.348



CNV
Annotation

CNV type	Disease	Platform	Pubmed
Deletion	Medulloblastoma	SNP arrays	21979893
Loss	Glioblastoma multiforme	CGH	19960244
Loss	Glioblastoma multiforme	conventional CGH	21080181
Loss	Glioblastoma multiforme	aCGH	21080181
Loss	Medulloblastoma	CGH	16968546

Copy Number Variation



Copy Number Variation

Ch r	Start	End	Normal Depth	Tumor Depth	Log Ratio
11	74113323	7411334 2	24.0	4.0	-2.559



CNV
Annotation
Platform

CNV type	Disease	Platform	Pubmed
Deletion	Medulloblastoma	SNP arrays	21979893
Loss	Glioblastoma multiforme	CGH	19960244
Loss	Glioblastoma multiforme	conventional CGH	21080181
Loss	Glioblastoma multiforme	aCGH	21080181

Copy Number Variation



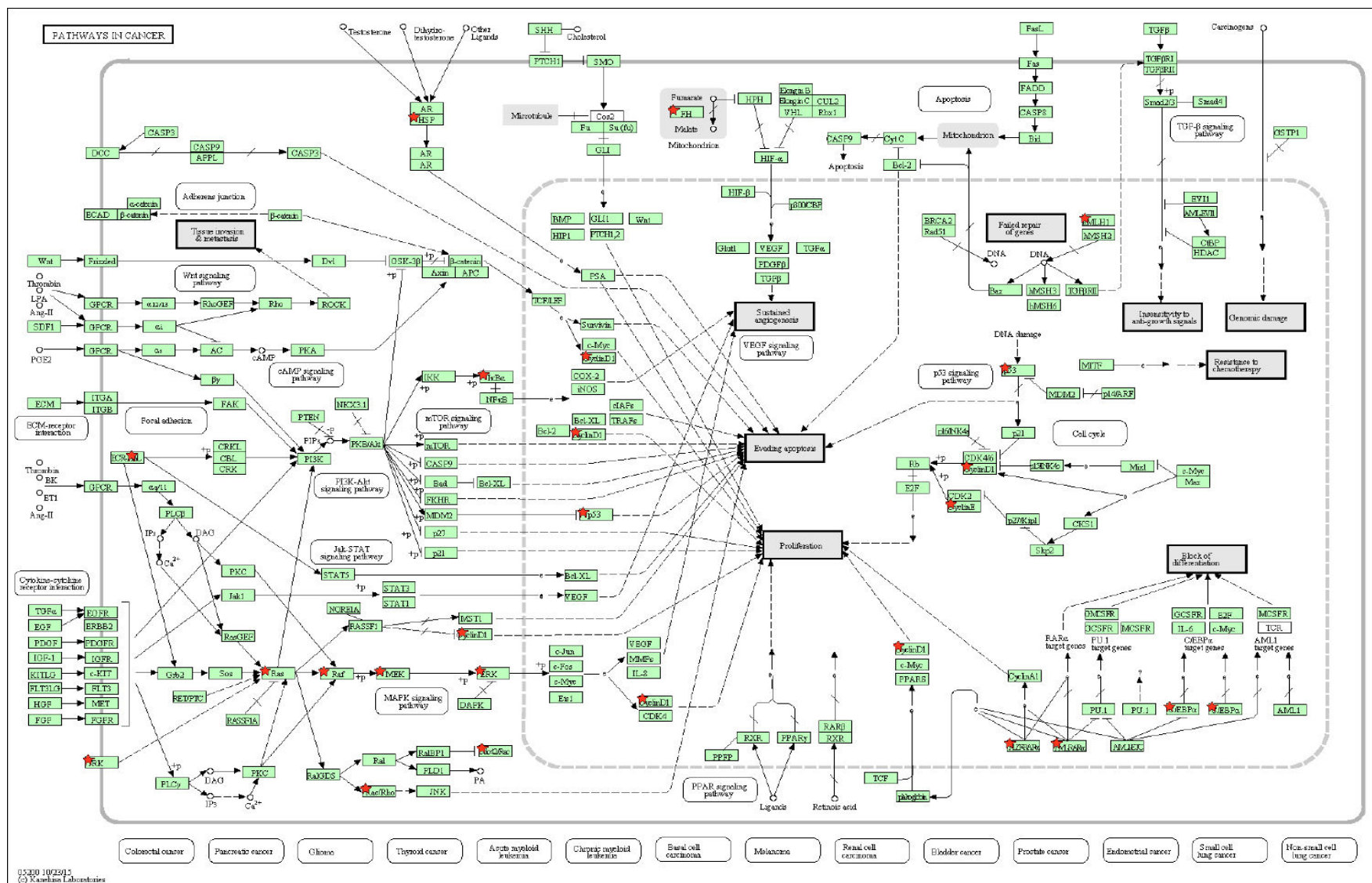
Scoring Algorithm

- Scoring system to identify major pathways leading to tumor progress
- Scoring System for targetable alterations in the tumor
- Scoring system for available drugs targeting most of the driver alterations

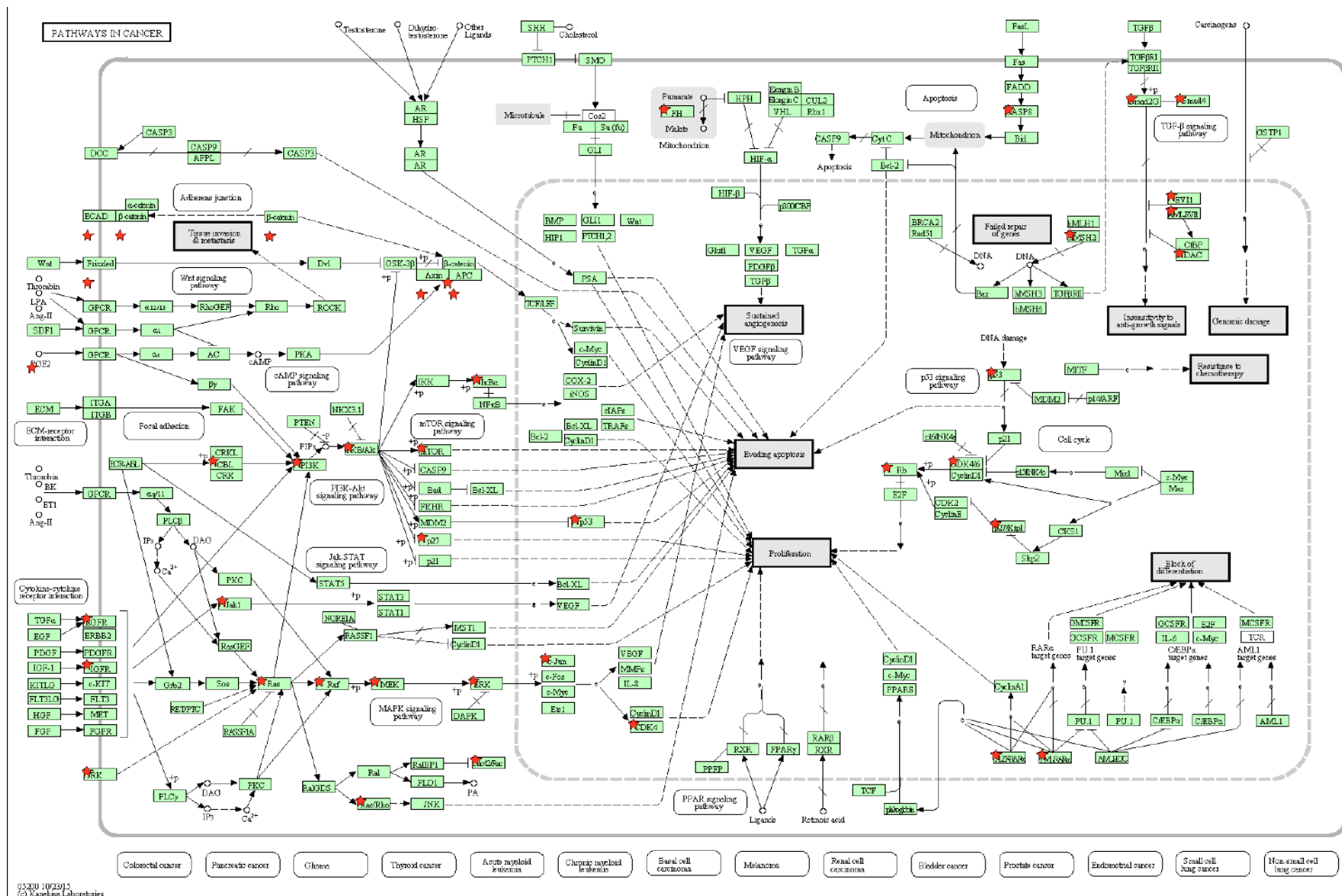
EXAMPLES of Exome Sequencing Data

- Patient 1 has CyclinD1 pathway over activated
- Patient 2 has Mtor pathway and CDK4 pathway activate
- Patient 3 has over amplification of Growth Factor receptors along with c-myc amplification
- Each has different driver mechanisms and requires different therapeutical scheme

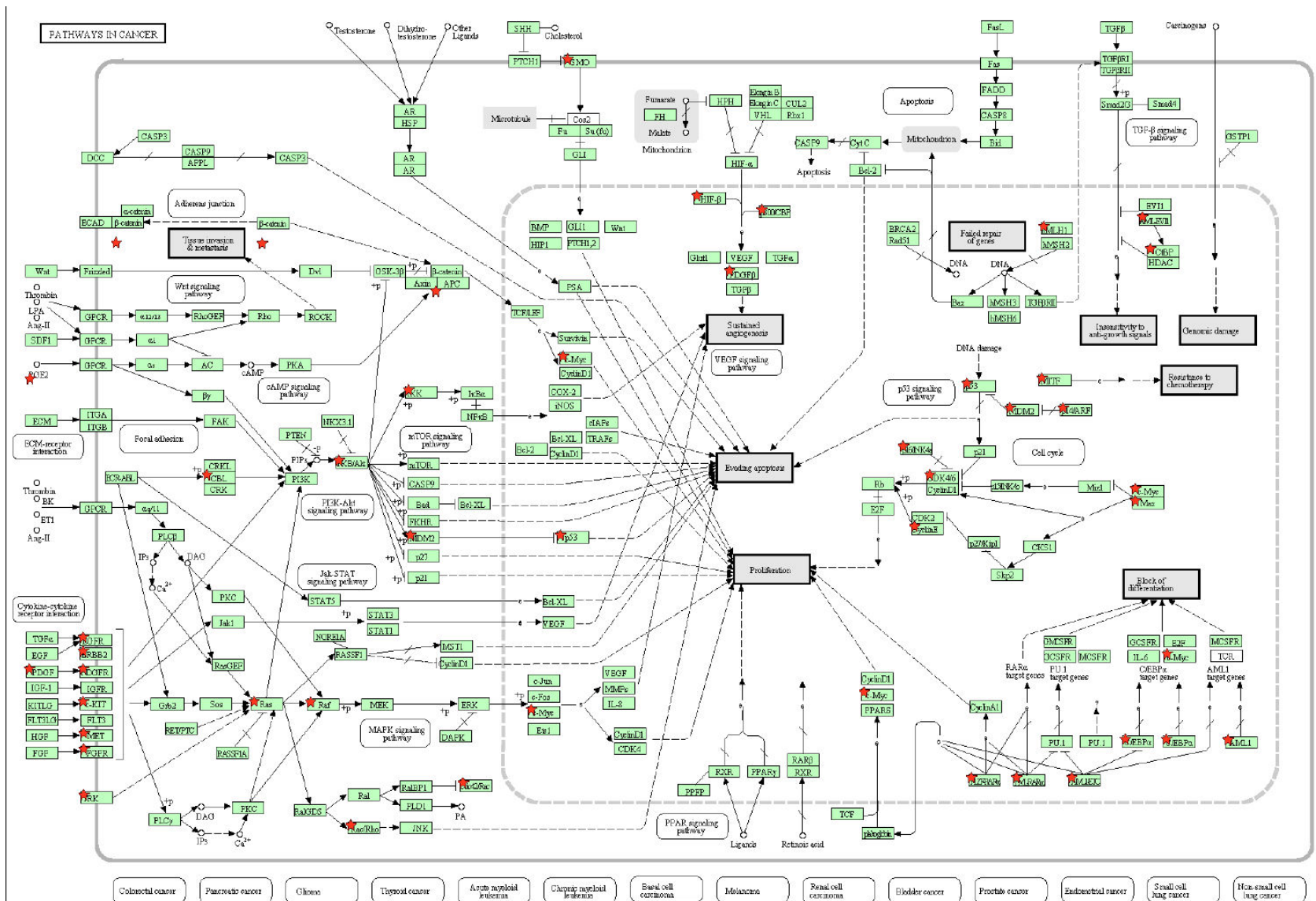
Patient 1



Patient 2



Patient 3



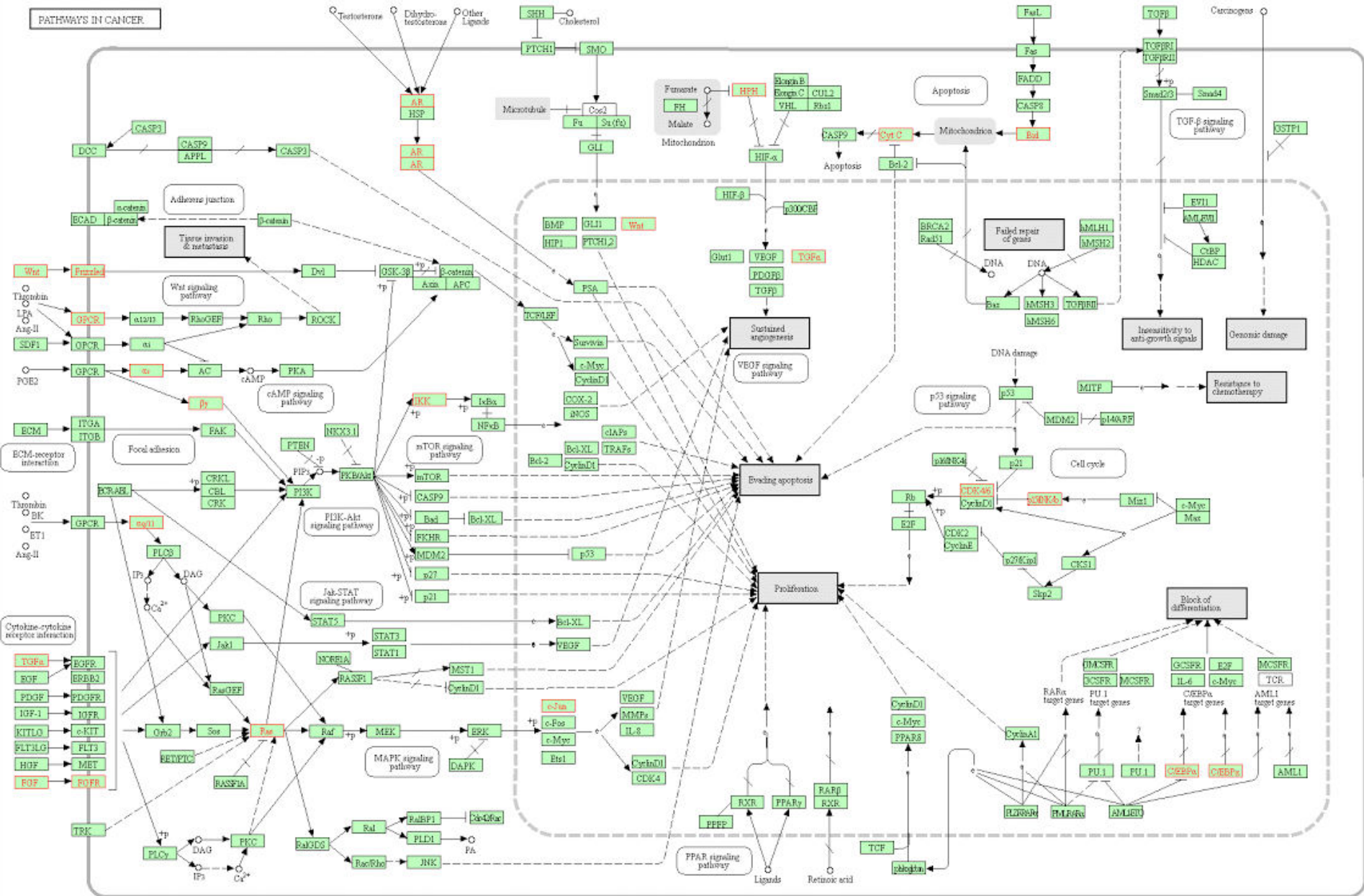
Genotyping for prevention Timoma (Sternum)Patient 4

- AMPD1 chr1 115236056_115236057
GA 192 snp rs17602729 Caa/Taa
Q/* protein_coding stop_gain stop_gained
HIGH pathogenic

Muscle_AMP_deaminase_deficiency|

Myestenia Gravis

PATHWAYS IN CANCER

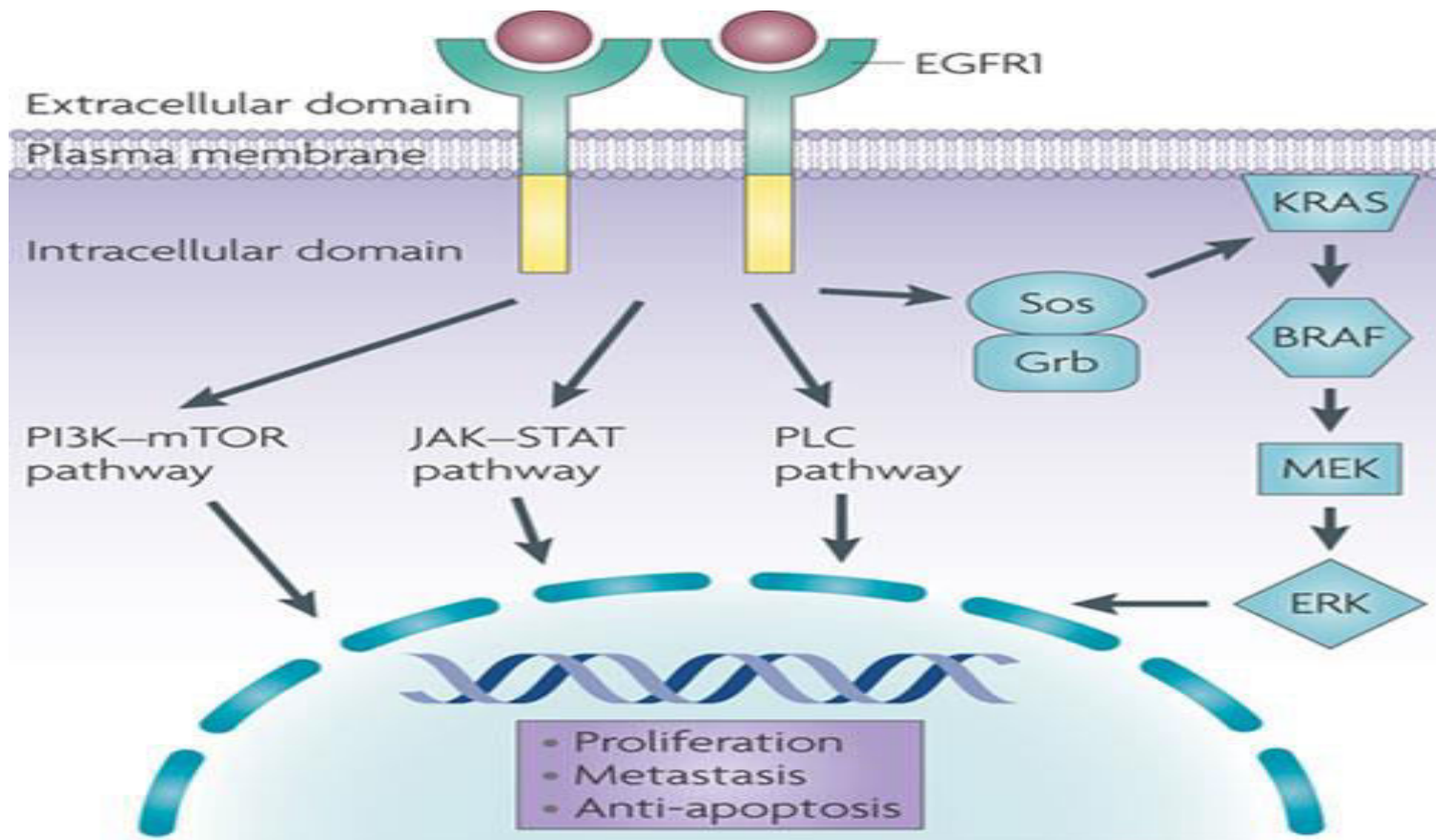


Colorectal cancer Pancreatic cancer Ovarian cancer Thyroid cancer Acute myeloid leukemia Chronic myeloid leukemia Basal cell carcinoma Melanoma Renal cell carcinoma Bladder cancer Prostate cancer Endometrial cancer Small cell lung cancer Non-small cell lung cancer

Target	Cancer	Variation type	Marker	Drug	Test
<i>EGFR</i>	Lung cancer	Mutation	Predict benefit to EGFR TKIs	Erlotinib	DNA
				Gefitinib	
<i>ALK</i>	Lung cancer	Rearrangement	Predict response to ALK inhibitors	Crizotinib	FISH
<i>ROS</i>	Lung cancer	Rearrangement	Predict response to TKIs	Crizotinib	FISH
<i>RET</i>	Lung cancer	Rearrangement	Predict response to TKIs	Vandetanib	FISH
<i>BRAF</i>	Melanoma	Mutation	Predict response to BRAF inhibitors	Vemurafenib	DNA
				Dabrafenib	
<i>KRAS</i>	Colorectal cancer	Mutation	Predict lack of response to anti-EGFR antibodies	Panitumumab	DNA
				Cetuximab	
<i>HER2</i>	Breast cancer	Amplification	Predict response to anti-HER2 antibodies	Trastuzumab	FISH, IHC
	Gastric cancer	Overexpression		Lapatinib	
				Pertuzumab	
<i>KIT</i>	GIST	Mutation	Predict response to c-Kit inhibitors	Imatinib	IHC
<i>Estrogen receptor</i>	Breast cancer	Overexpression	Predict response	Examestane	IHC
				Fulvestrant	
				Letrozole	
<i>Progesterone receptor</i>	Breast cancer	Overexpression	Predict response	Tamoxifen	
				Examestane	IHC
				Letrozole	

Personalized Treatment

Imatinib



- THANKS to
- Burcu Bakır Gungor
- Ozan Ozisik

Türk 100.000 Genom projesi

- Türkiye insan genomunun yapısının anlaşılması
- Türk genom veri analizi ile yeni bilimsel buluşlar ve tıbbi uygulamaların gerçekleştirilmesi
- Türkiye'de genomik tıbbın uygulamalarını hızlandırılması
- Sağlık hizmetlerinde etkin uygulamalar geliştirilmesi
- Genomik veriye dayalı Endüstriyi ve yatırımları başlatılması
- Uluslararası bölgede (Balkanlar ve Türki devletleri) örnek ve referans merkez olmak

Süreç Bilgilendirilmesi ve Değerlendirilmesi

Genom ve Biyoenformatik Bilim Kurulu

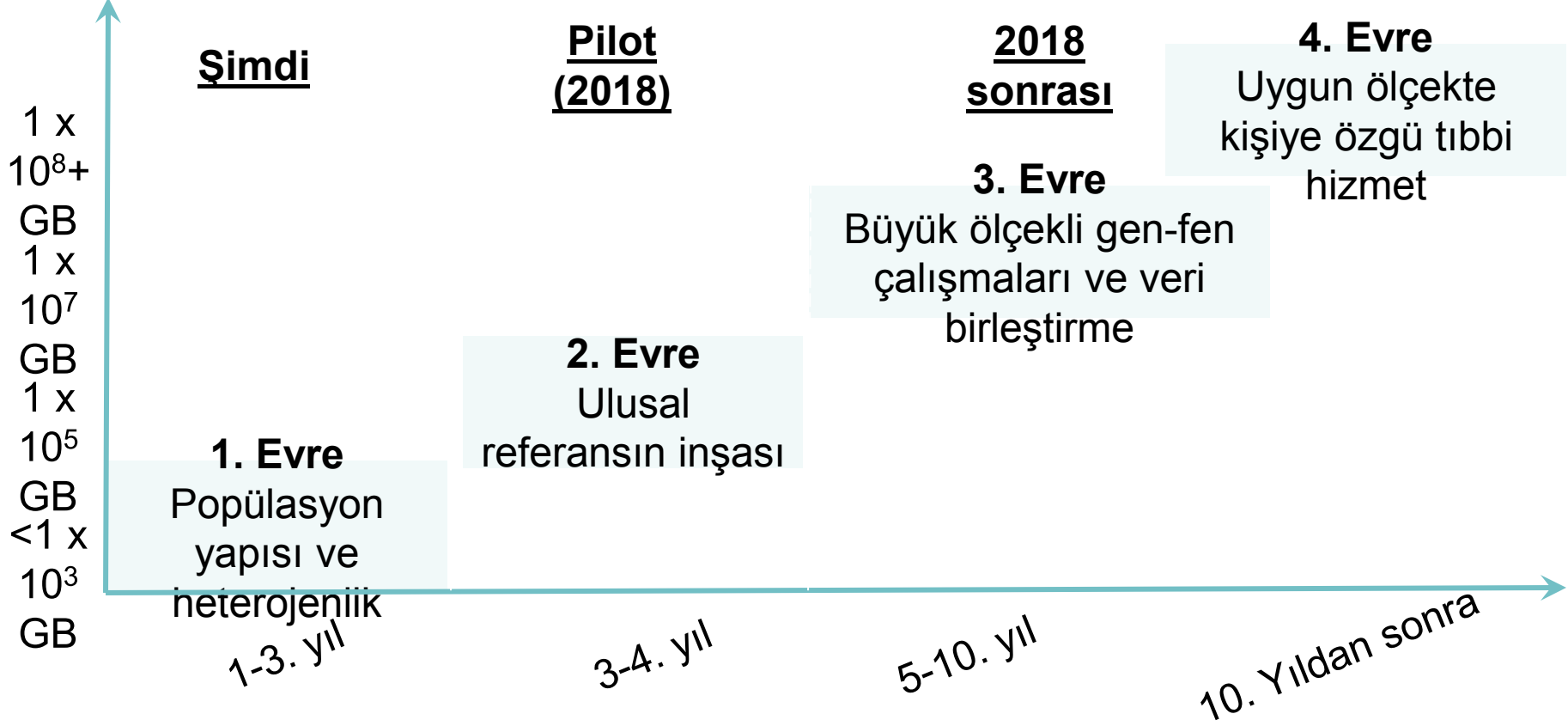
1. Prof. Dr. Yasemin ALANAY, Acıbadem Ü.
2. Y. Doç. Dr. Can ALKAN, Bilkent Ü.
3. Prof. Dr. Safiye Neşe ATABEY, Dokuz Eylül Ü.
4. Prof. Dr. Rengül Çetin-ATALAY, ODTÜ.
5. Av. Ahmet Esad BERKTAŞ, T.C. Sağlık Bak.
6. Prof. Dr. Hakan CANGÜL, Medipol Ü.
7. Prof. Dr. Pervin DİNÇER, Hacettepe Ü.
8. Doç. Dr. Devrim GÖZÜAÇIK, Sabancı Ü.
9. Prof. Dr. Ersan KALAY, Karadeniz Teknik Ü.
10. Prof. Dr. Ali O. KILIÇ, Karadeniz Teknik Ü.
11. Prof. Dr. M. Hamza MÜSLÜMANOĞLU,
12. Prof. Dr. Fatih ÖZALTIN, Hacettepe Ü.
13. Prof. Dr. Uğur ÖZBEK, Acıbadem Ü.
14. Y. Doç. Dr. Arif Barış ÖZBİLEN, Bilkent Ü.
15. Prof. Dr. Tayfun ÖZÇELİK, Bilkent Ü.
16. Prof. Dr. Hilal ÖZDAĞ, Ankara Ü.
17. Prof. Dr. Meral ÖZGÜÇ, Hacettepe Ü.
18. Prof. Dr. Rıza Köksal ÖZGÜL, Hacettepe Ü.
19. Prof. Dr. Ferda ÖZKINAY, Ege Ü.
20. Prof. Dr. Yusuf ÖZKUL, Erciyes Ü.
21. Y. Doç. Dr. Aslıhan ÖZTEZEL, İst. Aydın Ü.
22. Prof. Dr. Mehmet ÖZTÜRK, Dokuz Eylül Ü.
23. Prof. Dr. Emriye Ferda PERÇİN, Gazi Ü.
24. Prof. Dr. O. Uğur SEZERMAN, Acıbadem Ü.
25. Doç. Dr. Efe SEZGİN, İYTE
26. Doç. Dr. Yeşim Aydın SON, ODTÜ.
27. Prof. Dr. Şaban TEKİN, TUBİTAK-MAM
28. Prof. Dr. Sinan TÜRKYILMAZ, Hacettepe Ü.
29. Doç. Dr. Şükrü TÜZMEN, Doğu Akdeniz Ü.

Süreç Bilgilendirilmesi ve Değerlendirilmesi

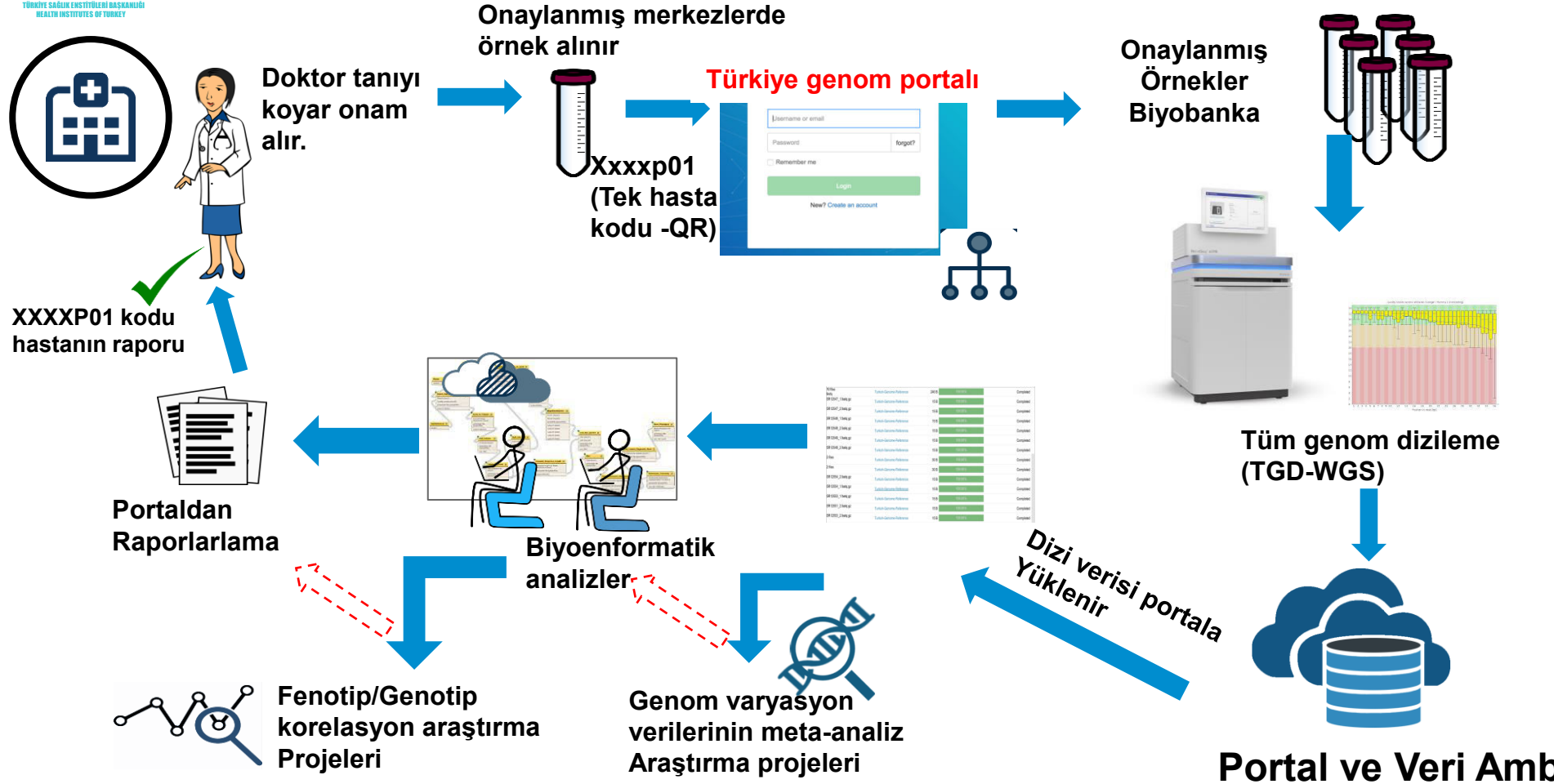
1. • ETİK ve HUKUK
2. • ÖRNEKLEME
3. • BİYOBANKALAR
4. • DİZİLEME MERKEZİ
5. • BİYOENFORMATİK

PİLOT DENEMENİN ÖTESİ: TÜRK GENOM PROGRAMININ GELECEĞİ

Veritabanı
büyüklüğü



Süreç Bilgilendirilmesi ve Değerlendirilmesi



Süreç Bilgilendirilmesi ve Değerlendirilmesi

Türkiye Genom Projesi Başlangıç Aşaması için Hizmet Alımı

TGP başlangıç aşamasında 100 000 genom için ölçeklenebilir Türkiye Genom projesi dizileme platformu ve veri paylaşım portalının 100 sağlıklı bireyden elde edilecek referans genom grafiği kapsamında işlevsel halde gerçekleştirilmesi

“Eksik teşhis konmuş sağlıklılar”

40 yaş üzerinde, bilinci yerinde, mental retarde olmayan, kendisinde ve 1. Derece akrabalarında (anne-baba-kardeş ve çocukları) kalıtsal hastalığı olmayan bireyler

TGP kapsamında çalışılması planlanan hastalık gruplarının belirlenmesi

ÖNCELİK : Nadir hastalıklar

- Nadir hastalıkların ~%80'i tek gen hastalığı,
- Az sayıda genom dizisi ile (1000-2000) ile yeni hastalık genleri keşfedilebilir,
-
- Hastalık yükü belirgindir (finansal maliyet, mortalite, morbidite)
SMA gen tedavisi ~3-4M TL/hasta
“En çok engellik veren ve en çok öldüren hastalıklardır”
- Toplumun %10'un da nadir hastalıklar gözlemleniyor (Türkiye'de ~7 milyon)
- Ulusal sosyolojik yapı (akraba evlilikleri) diğer genom projelerine göre Türkiye Genom Projesi açısından fark yaratacaktır

TGP kapsamında çalışılması planlanan hastalık gruplarının belirlenmesi

ÖNCELİK : Nadir hastalıklar

- Ulusal Kohortlara katılacak örnekleri belirlemek amacıyla değişik hastalıklar için genom projesine dahil edilme protokolleri “Human Phenotype Ontology” vb. rehberliğinde belirlenebilir
- Genom projesi dahil edilme algoritması ile uygun veya yetersiz tanı alan örneklerin belirlenerek biyobankalarda kataloglanabilir
- Fenotip varyasyon tanımlarının hekimlere portal üzerinden sunulabilir ve örnekler bu kapsamda projeye dahil edilebilir

Genom Çalışmalarının Fonlanması

Çağrılı projeler

- Çok ortaklı konsorsiyum projeleri
- Merkezler destekleri (Merkez kurulması destek veya alt yapı projeleri ile)
- Hastalık temalı disiplinler arası projeler
- Özelleşmiş biyoenformatik veri analizi projeleri
- Hesaplamalı Biyoloji/algoritma geliştirme projeleri
- Genom analiz teknolojileri ve tanı/tedavi/takip araçları geliştirme

projeleri

- Çığır açıcı projeler

Proje destek süresi

- Proje çağrısının kapsamına göre 1-5 yıllık
- Proje başarı oranına göre süresi artırılabilen aşamalı projeler

Kohort çalışmalarında klinik tahlil ve testlerin fonlanması

-Kohort çalışmalarında hastalara ait tamamlayıcı klinik verilerin (klinik testler) fonlanması

-Klinik verilerin tamamlanması için projelendirmede mevzuat düzenlemesi gerekebilir.