Fundamentos de la Genética en la Medicina Personalizada de Precisión

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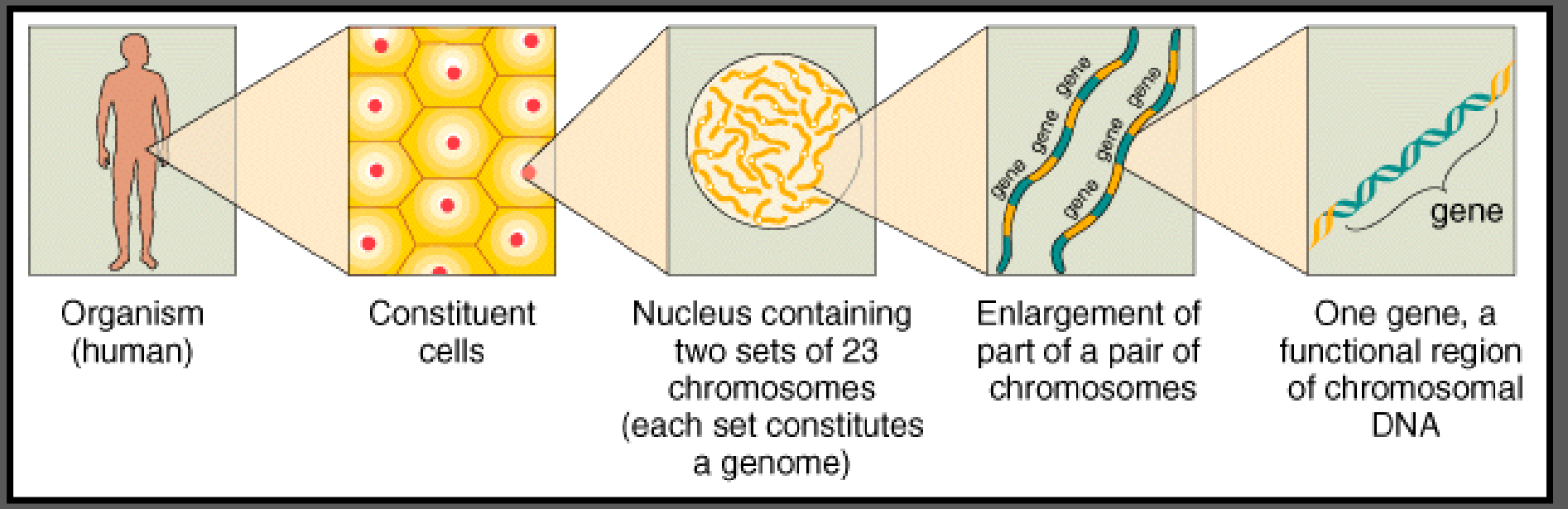
Medicina Personalizada de Precisión: de la teoría a la práctica

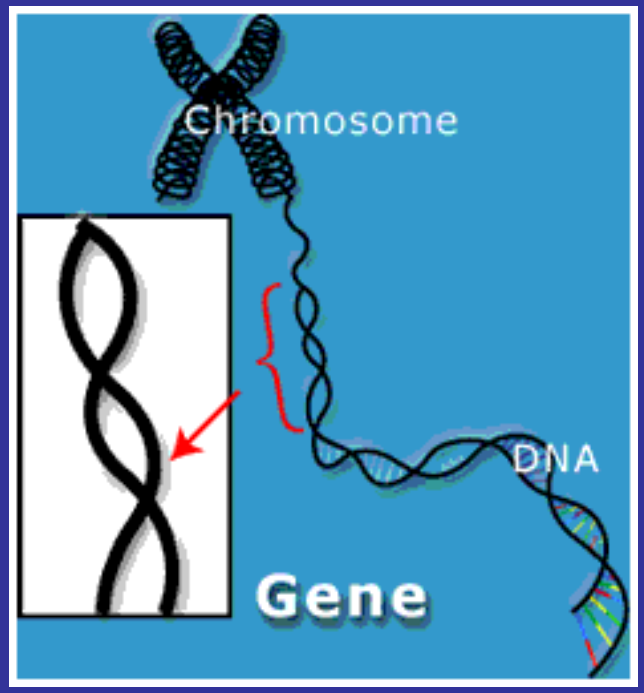
@MPAlonso

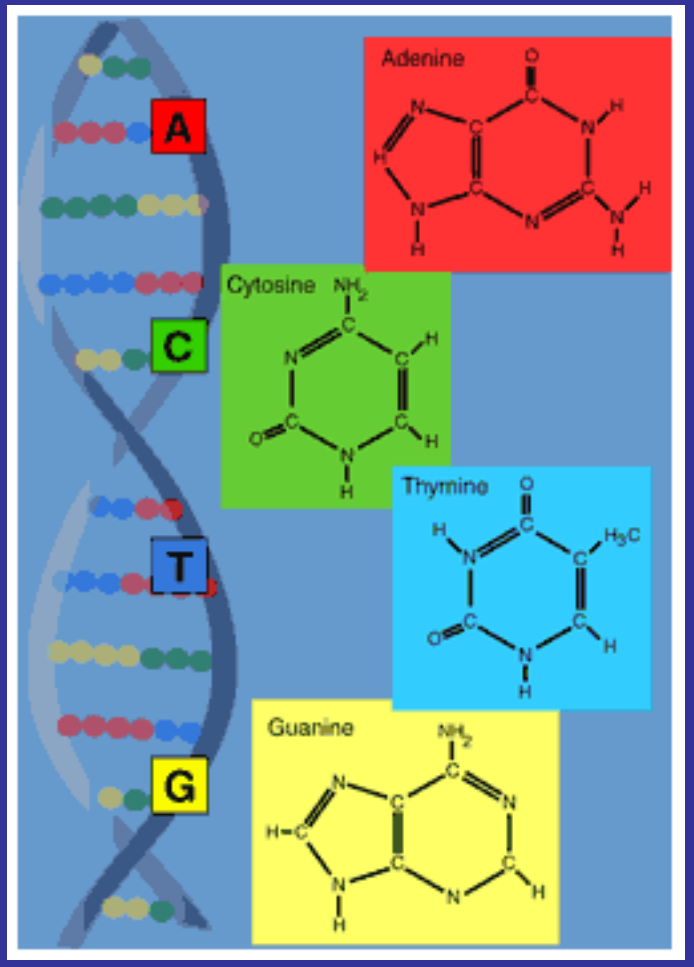
Docencia e investigación en Genética y Genómica en la Universitat de València

Los genes y el genoma

Dos genomas en cada una de nuestras células




Chromosome
DNA
Gene


A
C
T
G
Adenine
Cytosine
Thymine
Guanine

El genoma es una biblioteca

GAATTCGCCGGTTAGGTTTTAGTATCAAGAAGAGAAGGAAATTTTGGACAGTGAATGGGC
AATAAATGTGAGTAATATGGGAAATAAATGAATTTAAGAGGATTTGTTGTGATCGTTATT
ATATGCGTGAAAGTCTTTAAATGCGTTTTTCCTTTTTCTTCACCATAAACCTTCTAGTTC
ATATAGAGGGACCACGTCCCACATGTTCTCCAAAATGTACATTCGTTCTAACATTCAAAT
TTCACGAGATTTCATTTAGGTTTAAATTGAGCTTAAATTGTTGTGTATATATAGTACTAG
TGCAAGTTTGATCGGTTATTTTTCTTTACTAATTGACATACTTGTCGTTGTCGTAAAAAA
CATGGATTGTTTATTTGTTTATATCAATTTGTTTGCACCAACCACCACAAGAAAATTAGT
TTTGATCGGCCAGTTTAATACAAAGTCCACTTCATATGATACTTATTTCTTTCATAATTT
GTTAGCCCCTCTGATTATTATTATGTACAACATCATTATTTTGCTTGAAAATATATATAT
CCAAGAGTCTTTGGAAGTCCTTGTTCAAACATTGGCAATGGGTTCTAAAATGTAAGAGTT
TCGACCTGAGATTTTCTCCGGGATGTATATCACATTATAGTTATGAATGTCTAATATATT
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TGATGTCTCAAATCCAAGGTATCATTTGAAAACTACAATTTGACCTGCAAAATGAAAAAG
CTCAAAGAAATCATGAAACAAGACAAGAAACCGAAACATATCAAAAGATTAAGATCAATG
ACGCAAAAGATTCGCTATCGATGAAAGGAGCGAAACCATGAAGCAAGATAGGTTGTAGAT
GAACTAGGAAAGGTTGAAGATGGACTAATTTTGTACTGGAAAAGGTGACGGTATAGACCT
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CTAGTGCATCGTGTTTTTGAAAATCGAATCTAAAAAGGCAGAATATATGAATTGAAACAC
AACTCTATTTAAATTAATATATCATCCAAACGTTATGCTTTTGTTTCTCTCAAAAATAAA
AGTTCTAAATTGCATGATACAAAACTTCTCTAAATTGCATGATACAGCTAGCCTATTACA
ACATGAGAATACCAACTATATCAGTGTAGTCGTTTTGTTTTTACCTCTTTCGCTAAACTG
ATTGCATCCAAGAATGAATTAACTTTTACTAGGCCAGAAGTGTAGCTAACATAGAAGAGG
CCCATTATAAAACTCTTTAAAATCAAAATCTAAAACAGGCCCAGCCCATTCATAACAAAG
CCCTAATATATCGAGTAAACCTAGCTCCACTCAAAACCTAACTATATAACCTTCACACAC

NCBI

NCBI Map Viewer

PubMed | Nucleotide | Protein | Genome | Gene | Structure | PopSet | Taxonomy | Help

Search for [ ] on chromosome(s) [ ] assembly [All] Find Advanced Search

Map Viewer
- Map Viewer Home
- Map Viewer Help
- Human Maps Help
- Release Notes

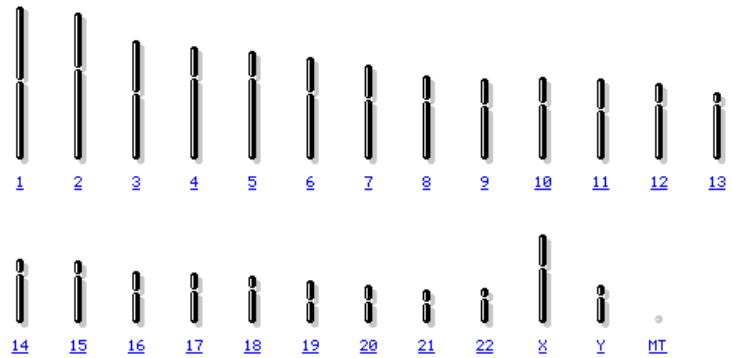
NCBI Resources
- Genome Project
- Trace Archive (Venter)
- RefSeq
- Whole Genome Association (WGA)
- Human Genome Resources
- GRC
- Consensus CoDing Sequence (CCDS)
- Trace FTP (Personal Genomics)
- NCBI Handbook
- Trace Archive (Watson)

Organism Data in GenBank
- EST
- Genomic

Homo sapiens (human) genome view

Build 37.2 statistics Switch to previous build

BLAST search the human genome



Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo; Homo sapiens

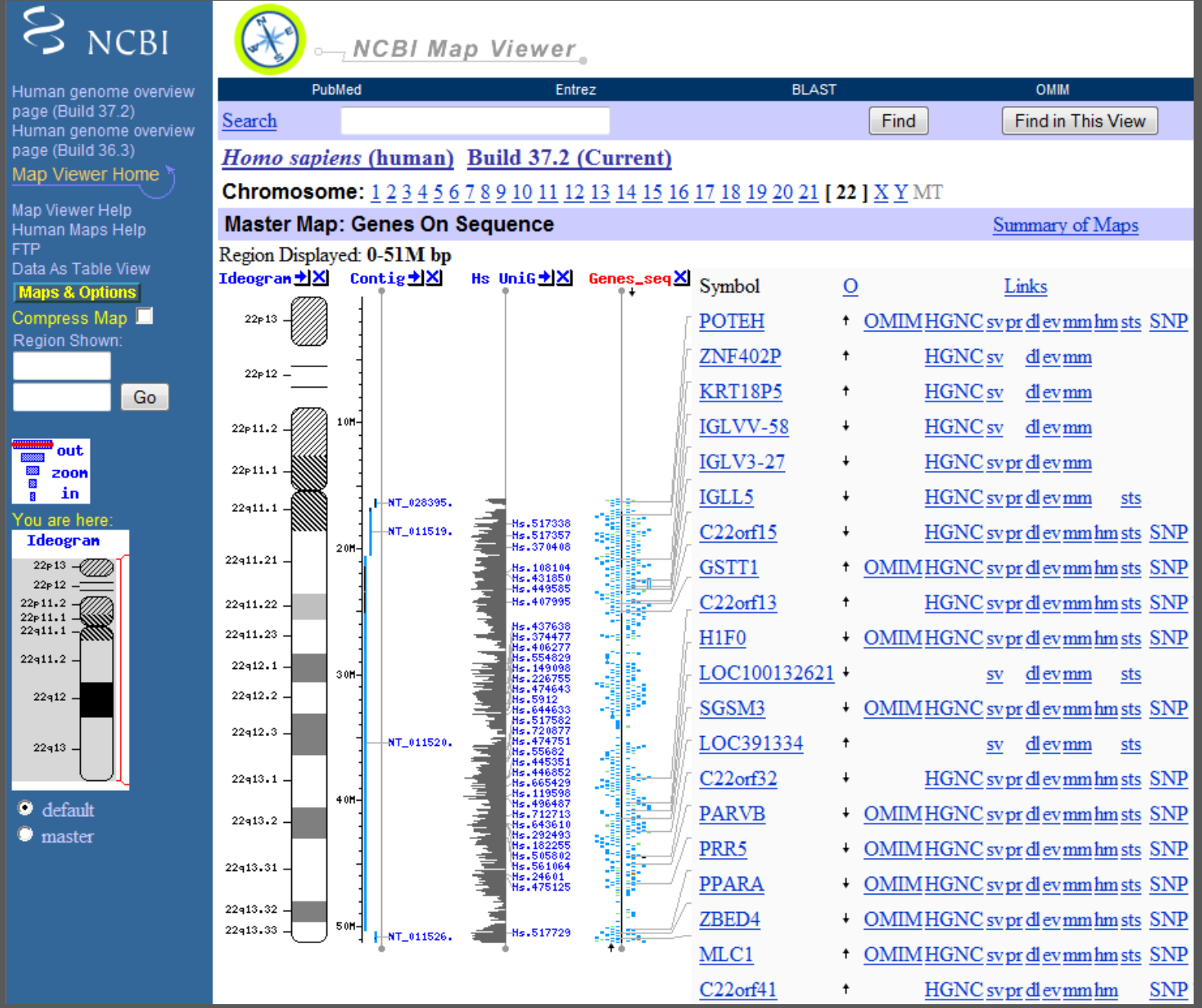
November 2010: NCBI released an incremental update of the human genome reference assembly and updated annotation for all assemblies. The chromosomes and alternate loci regions are not changed; the new assembly includes the second set of genomic region Patches released by the Genome Reference Consortium (Genome Reference Consortium (GRC)) and is named GRCh37.p2. A previous version of the reference genome assembly, NCBI Build 36.3, can still be accessed for Map Viewer display and for BLAST. For additional information about changes, statistics, and the status of the CCDS project please refer to:

- Release Notes
- Statistics
- CCDS Project

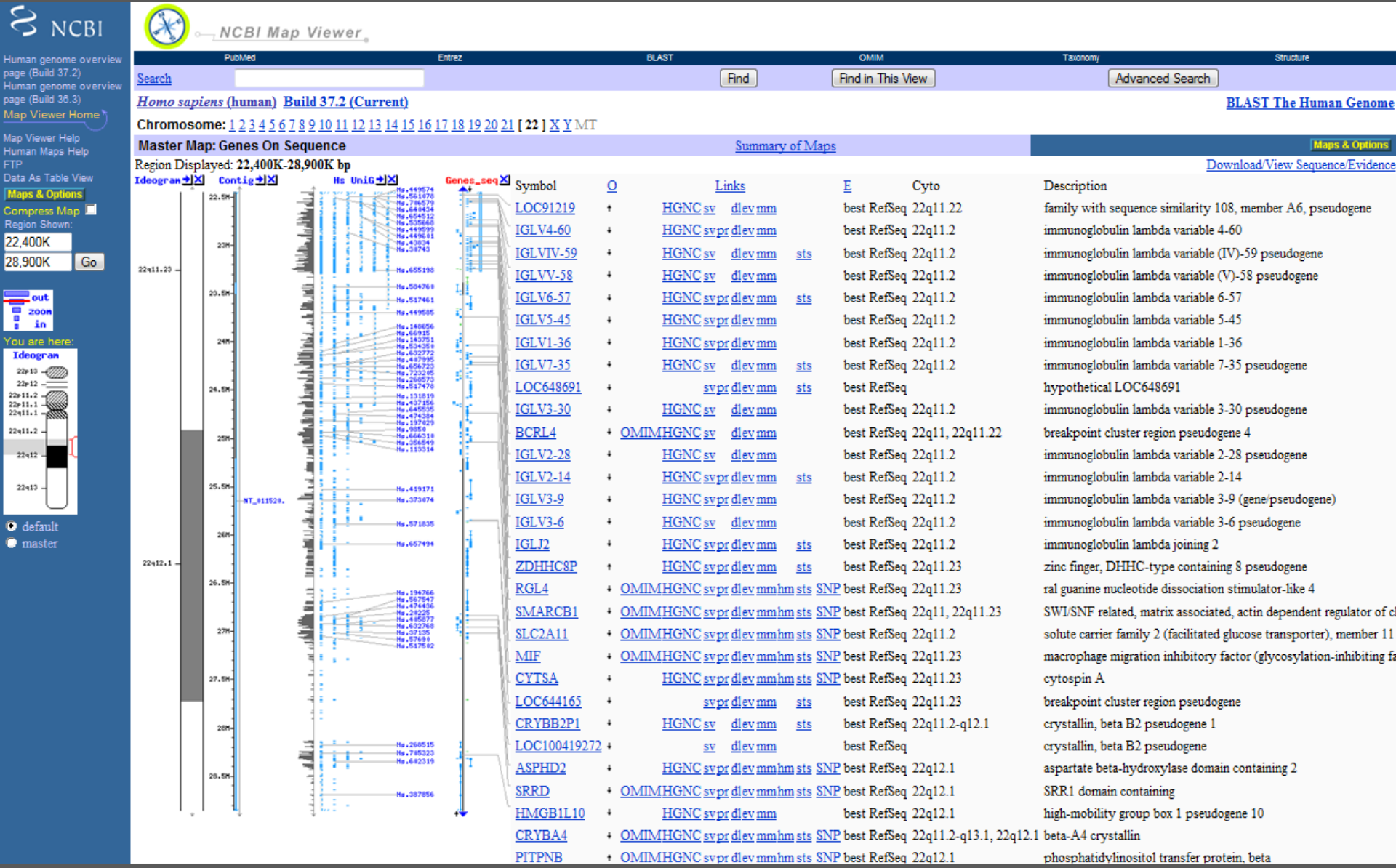
The NCBI Map Viewer provides graphical displays of features on the human genome sequence assembly as well as cytogenetic, genetic, physical, and radiation hybrid maps. Extensive documentation is provided to describe the resource features and methods used, tutorials, and statistics.

Map features that can be seen along the sequence include genes, transcripts, NCBI contigs (the 'Contig' map), the BAC tiling path (the 'Component' map), STSs, FISH mapped clones, ESTs and transcripts from several different organisms, Gnomon predicted gene models, and more.

www.ncbi.nlm.nih.gov/genome/guide/human



www.ncbi.nlm.nih.gov/genome/guide/human



www.ncbi.nlm.nih.gov/genome/guide/human

El tamaño del genoma humano

3.234 millones de pb = 3,2 Gb

21.000 genes, aprox

¿Cuántos genes tiene el genoma humano?

POR GENÉTICA MÉDICA · PUBLICADO EL 9 DE JULIO DE 2018 ·

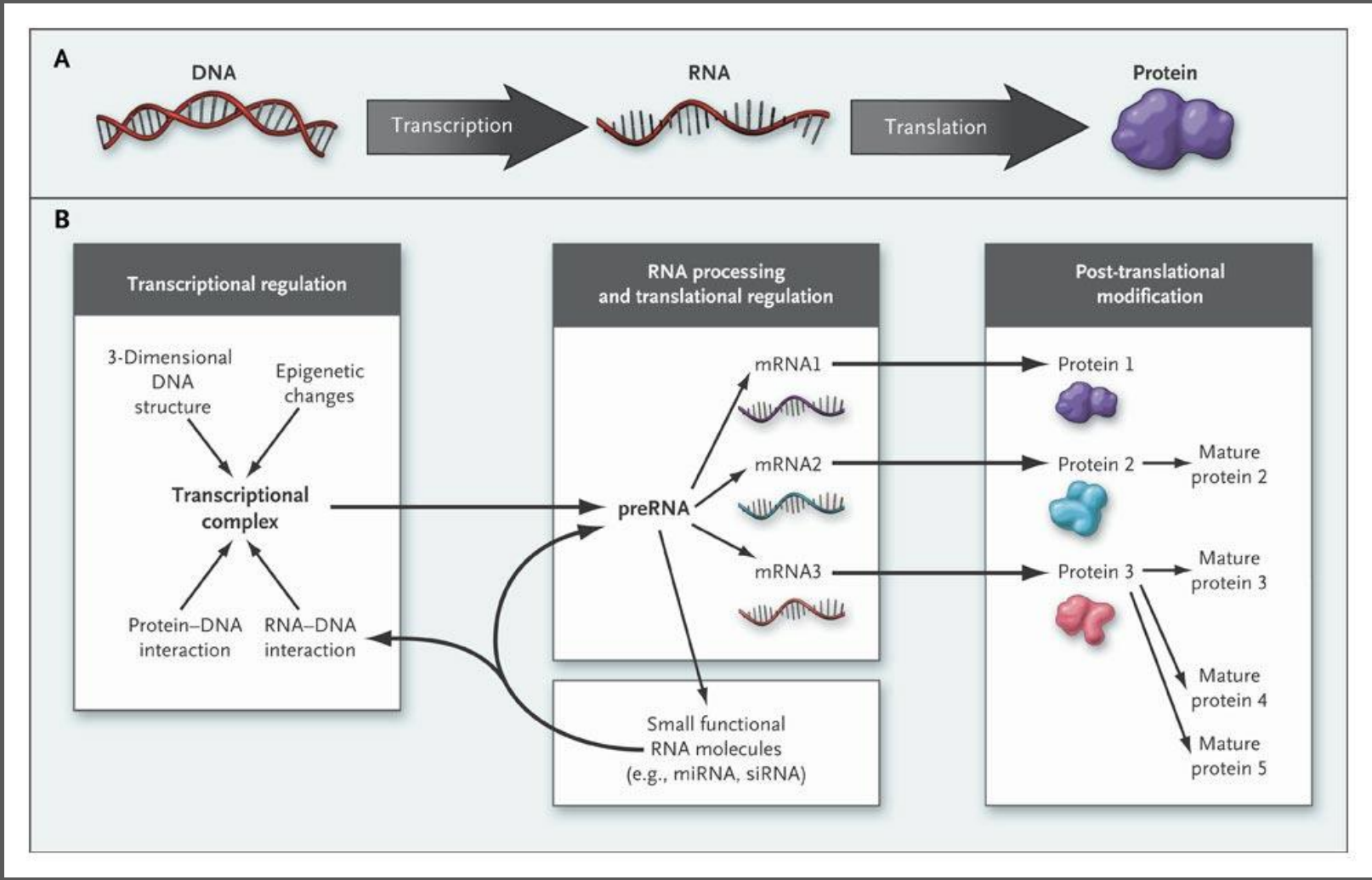
Amparo Tolosa, *Genética Médica News*

Desde los inicios del Proyecto Genoma Humano, allá por el año 1990, todo parecía indicar que la respuesta a una de las preguntas más relevantes de la Genética, la de **cuántos genes tiene el genoma humano**, estaba cerca.

Las primeras estimaciones previas a la secuenciación del genoma humano calculaban que había unos 100.000 genes. Sin embargo, para sorpresa de muchos, **el Proyecto Genoma Humano reveló que el número de genes que codifican para proteínas era sustancialmente menor de lo esperado: entre 30.000 y 35.000 genes**. Desde aquel primer borrador del genoma, publicado en 2001, el número de genes se ha ido reduciendo poco a poco y hace no tanto se hablaba de 19.000 genes codificantes para proteínas. Pero lo que es cierto es que todavía no hay un número oficial definitivo.

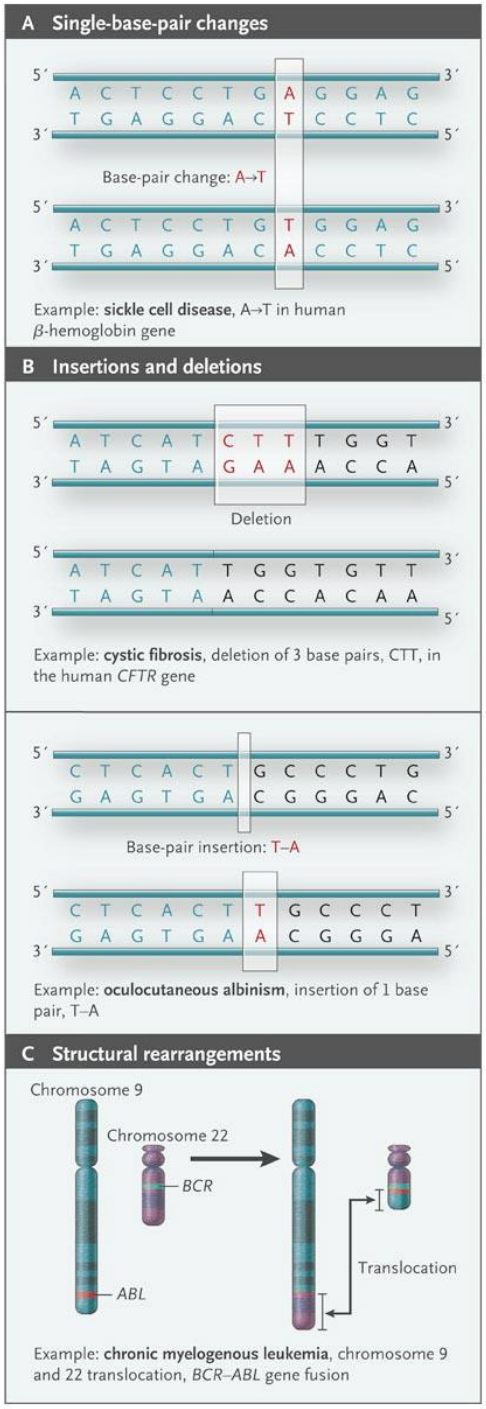
revistageneticamedica.com/2018/07/09/genes-genoma-humano/

Dogma Central expandido



Feero et al (2010). Genomic Medicine, an updated primer. N Engl J Med 362: 2001-11.

Enfermedades genéticas y diagnóstico genético



Mutaciones en el genoma humano

Feero et al (2010)
Genomic Medicine, an updated primer
N Engl J Med 362: 2001-2011.

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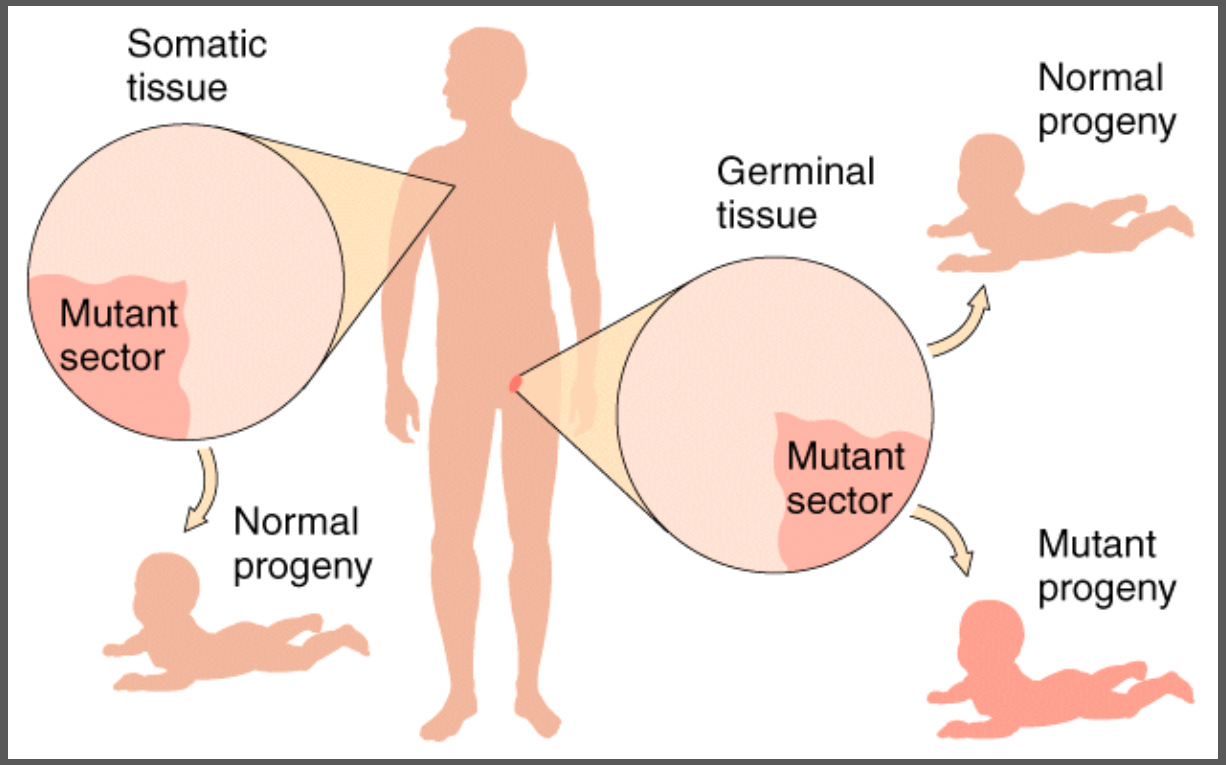
Mutaciones somáticas y mutaciones germinales

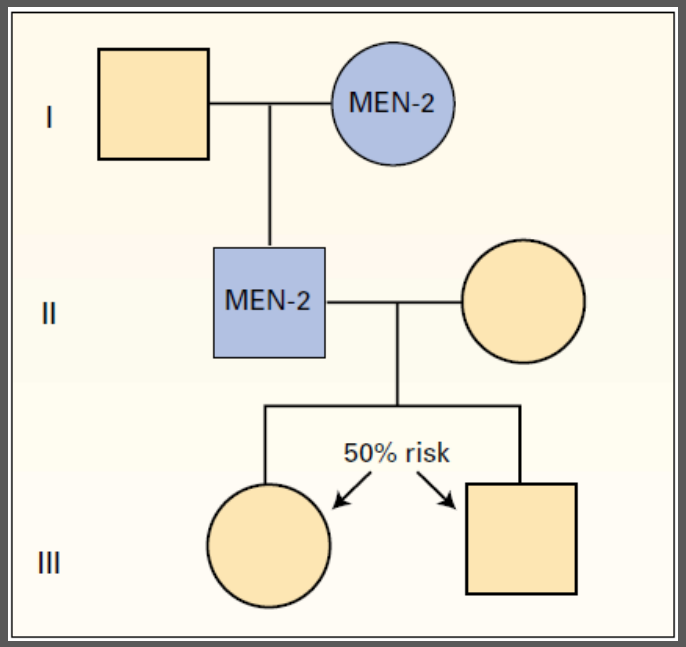


Dos tipos de herencia

- **Herencia mendeliana simple**: son enfermedades monogénicas (casi siempre enfermedades raras).

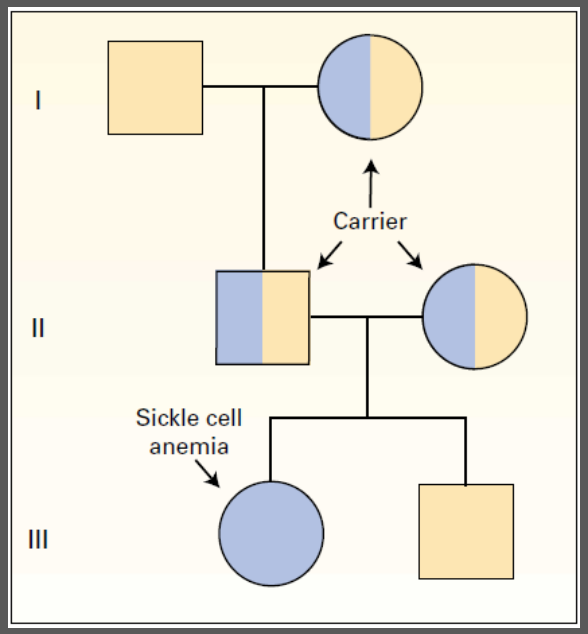
- **Herencia compleja**: son enfermedades multifactoriales (casi siempre enfermedades comunes, aunque algunas son enfermedades raras).

Herencia autosómica dominante



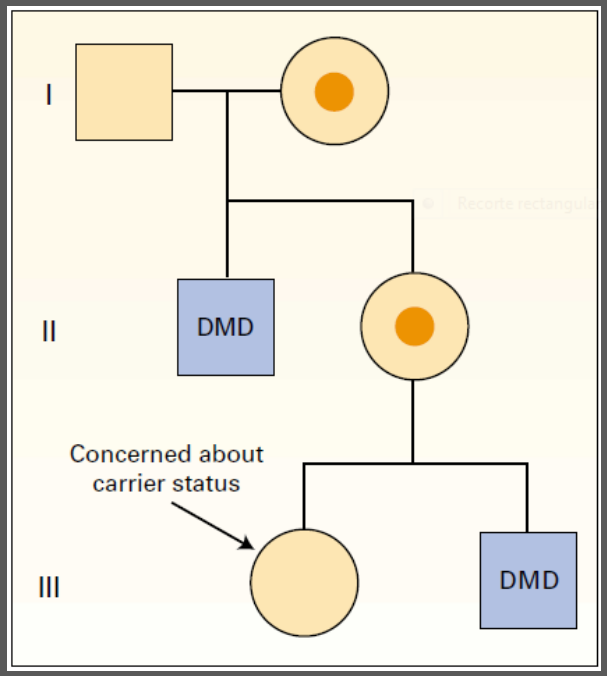
(Ej. Neoplasia endocrina múltiple)

Herencia autosómica recesiva



(Ej. Fibrosis quística)

Herencia recesiva ligada al X



(Ej. Distrofia muscular de Duchenne)

Ejemplos de enfermedades genéticas

Fibrosis quística
Hemofilia
Síndrome de Marfan
Talasemia
Poliquistosis renal
Distrofia miotónica
Retinitis pigmentosa
Ataxias hereditarias
Síndrome de Prader-Willi
Cáncer de mama y ovario
Osteogénesis imperfecta
Distrofia muscular de Duchenne
Enfermedad de Huntington
Neurofibromatosis
Enfermedad de Charcot-Marie-Tooth
Fenilcetonuria
Síndrome del X-frágil
Acondroplasia
Hemocromatosis
Hipercolesterolemia familiar
Neoplasia endocrina múltiple
Enfermedad de Alzheimer

Cerca de 8.000 enfermedades genéticas, de las cuales ya podemos diagnosticar unas 5.000 (analizando genes individuales)

NCBI

OMIM
Online Mendelian Inheritance in Man

Johns Hopkins University

My NCBI [Sign In] [Register]

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | PMC | OMIM

Search OMIM for [ ] Go Clear

Limits | Preview/Index | History | Clipboard | Details

Display Detailed Show 20 Send to

All: 1 | OMIM UniSTS: 0 | OMIM dbSNP: 0

MIM ID +113705

MGI, GeneTests, Links

BREAST CANCER 1 GENE; BRCA1

Other entities represented by this entry

PANCREATIC CANCER, SUSCEPTIBILITY TO, 4, INCLUDED; PNCA4, INCLUDED

Gene map locus: 17q21

Description

Back to Top

BRCA1 plays critical roles in DNA repair, cell cycle checkpoint control, and maintenance of genomic stability. BRCA1 forms several distinct complexes through association with different adaptor proteins, and each complex forms in a mutually exclusive manner (Wang et al., 2009).

Cloning

Back to Top

Miki et al. (1994) identified cDNA sequences corresponding to the BRCA1 gene by positional cloning of the region on 17q21 implicated in familial breast-ovarian cancer syndrome (604370). The deduced 1,863-residue protein with zinc-finger domains near the N terminus. A 7.8-kb mRNA transcript was identified in testes, thymus, breast and ovary. There appeared to be a complex pattern of alternative splicing.

Bennett et al. (1995) found that the mouse Brca1 gene shares 75% identity of the coding region with the human sequence at the nucleotide level, whereas the predicted amino acid identity was only 58%.

Jensen et al. (1996) demonstrated that BRCA1 encodes a 190-kD protein with sequence homology and biochemical analogy to members of the granin protein family, including chromogranin A (118910), chromogranin B (118920), and secretogranin II, also known as chromogranin C (118930). They noted that BRCA2 also includes a motif similar to the granin consensus at the C terminus of the protein. Both BRCA1 and the granins localize to secretory vesicles, are secreted by a regulated pathway, are posttranslationally glycosylated, and are responsive to hormones. The authors stated that as a regulated secretory protein, BRCA1 appears to function by a mechanism not previously described for tumor suppressor products. As reviewed by Steeg (1996), granins are a family of acidic proteins that bind calcium and aggregate in its presence. Known members of the granin family have been solely neuroendocrine or endocrine in origin; if BRCA1 is a granin it will necessarily expand the protein family boundaries.

Table of Contents

Links

Selected Gene Related Links
- Entrez Gene
- Nomenclature
- RefSeq
- GenBank
- Protein
- UniGene

Other NCBI Links
- BioSystems
- Books
- Free in PMC
- GEO Profiles
- Gene
- Gene Genotype
- GeneTests
- GeneView in dbSNP

www.ncbi.nlm.nih.gov/omim

Todo sobre nuestro genoma: OMIM

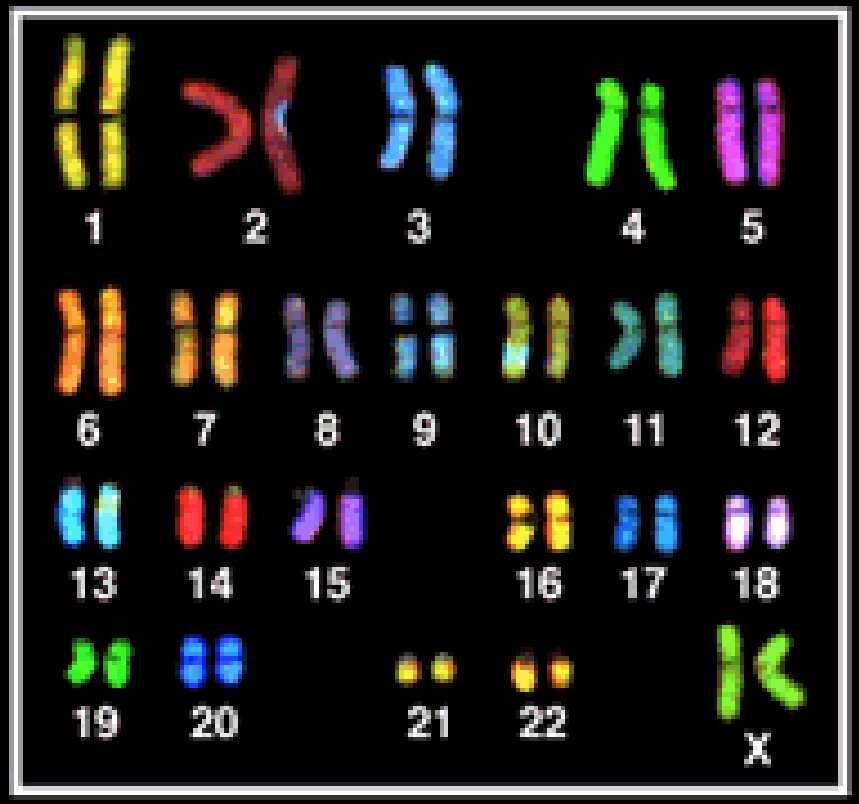
OMIM Entry Statistics

Number of Entries in OMIM (Updated September 12th, 2018) :

MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	15,153	730	49	35	15,967
Gene and phenotype, combined +	47	0	0	2	49
Phenotype description, molecular basis known #	4,960	327	4	31	5,322
Phenotype description or locus, molecular basis unknown %	1,450	124	4	0	1,578
Other, mainly phenotypes with suspected mendelian basis	1,656	105	3	0	1,764
Totals	23,266	1,286	60	68	24,680

omim.org/statistics/entry

Técnicas de diagnóstico genético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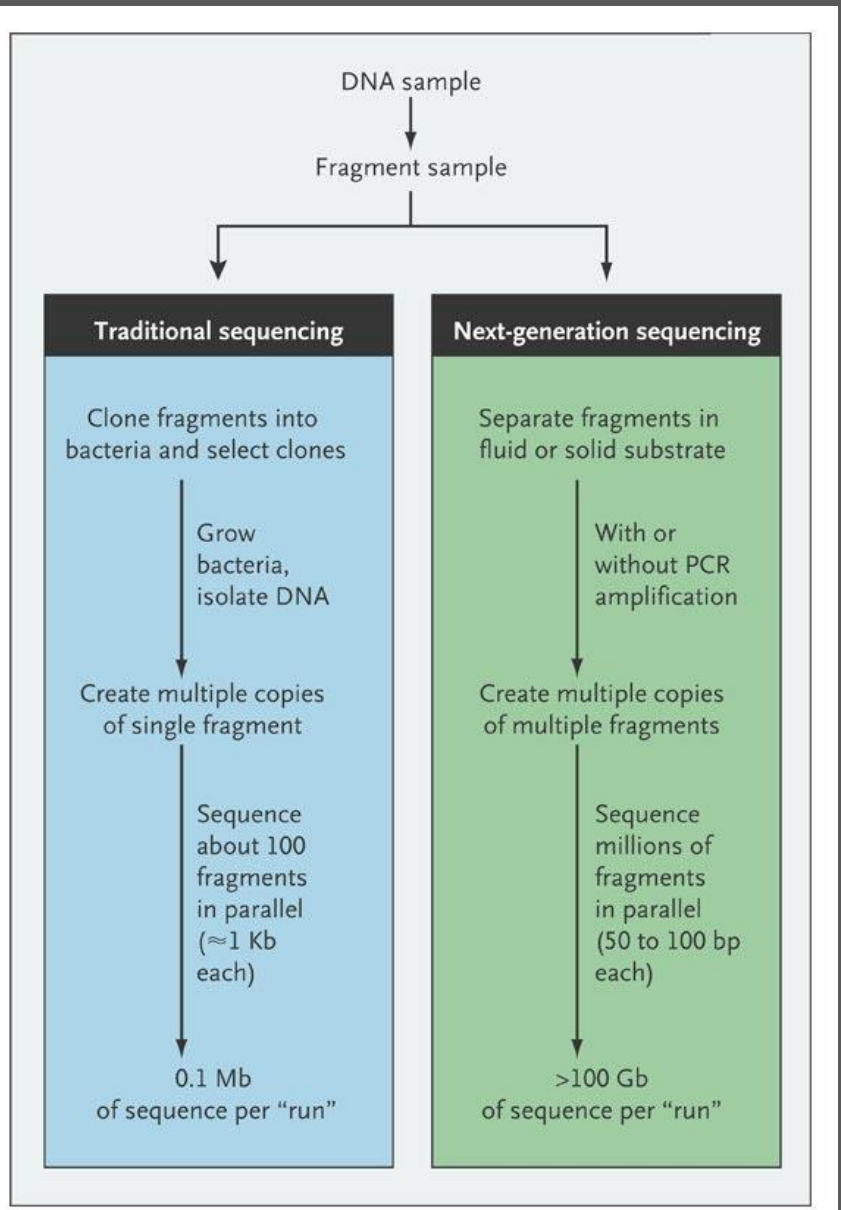
21
22
X

Técnicas de secuenciación de ADN



Secuenciación mediante el método de Sanger
vs
Secuenciación NGS

Feero et al (2010)
Genomic Medicine, an updated primer
N Engl J Med 362: 2001-2011

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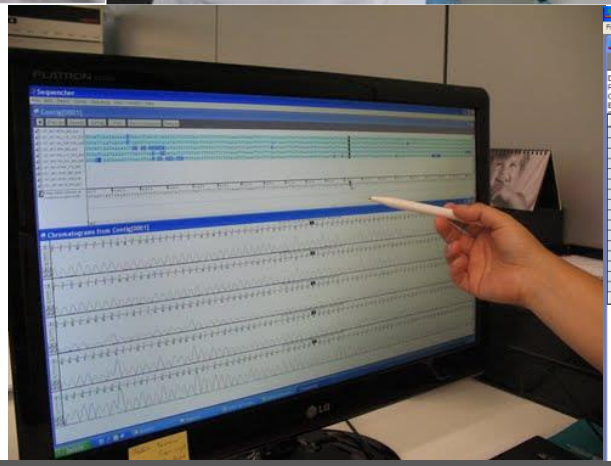
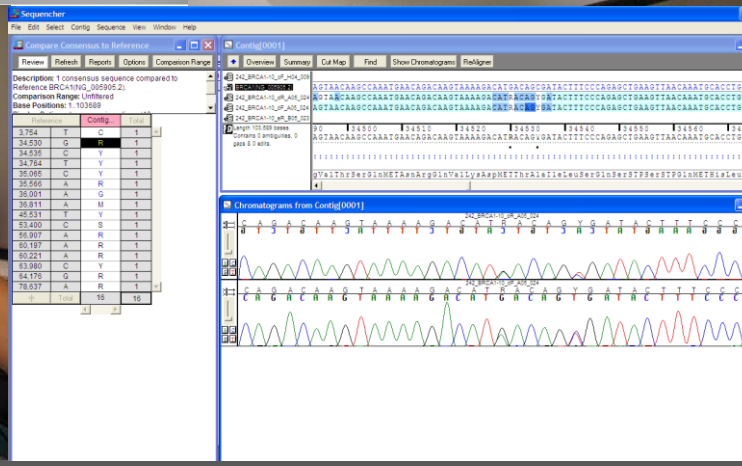
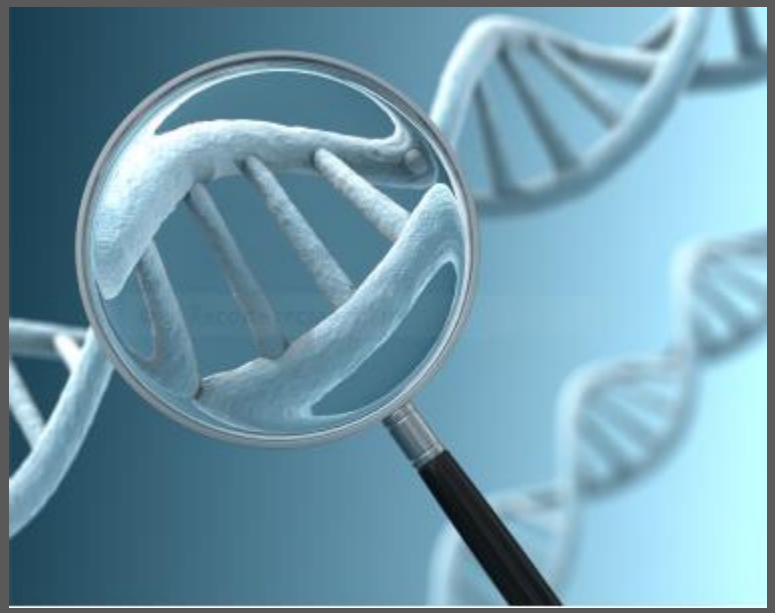
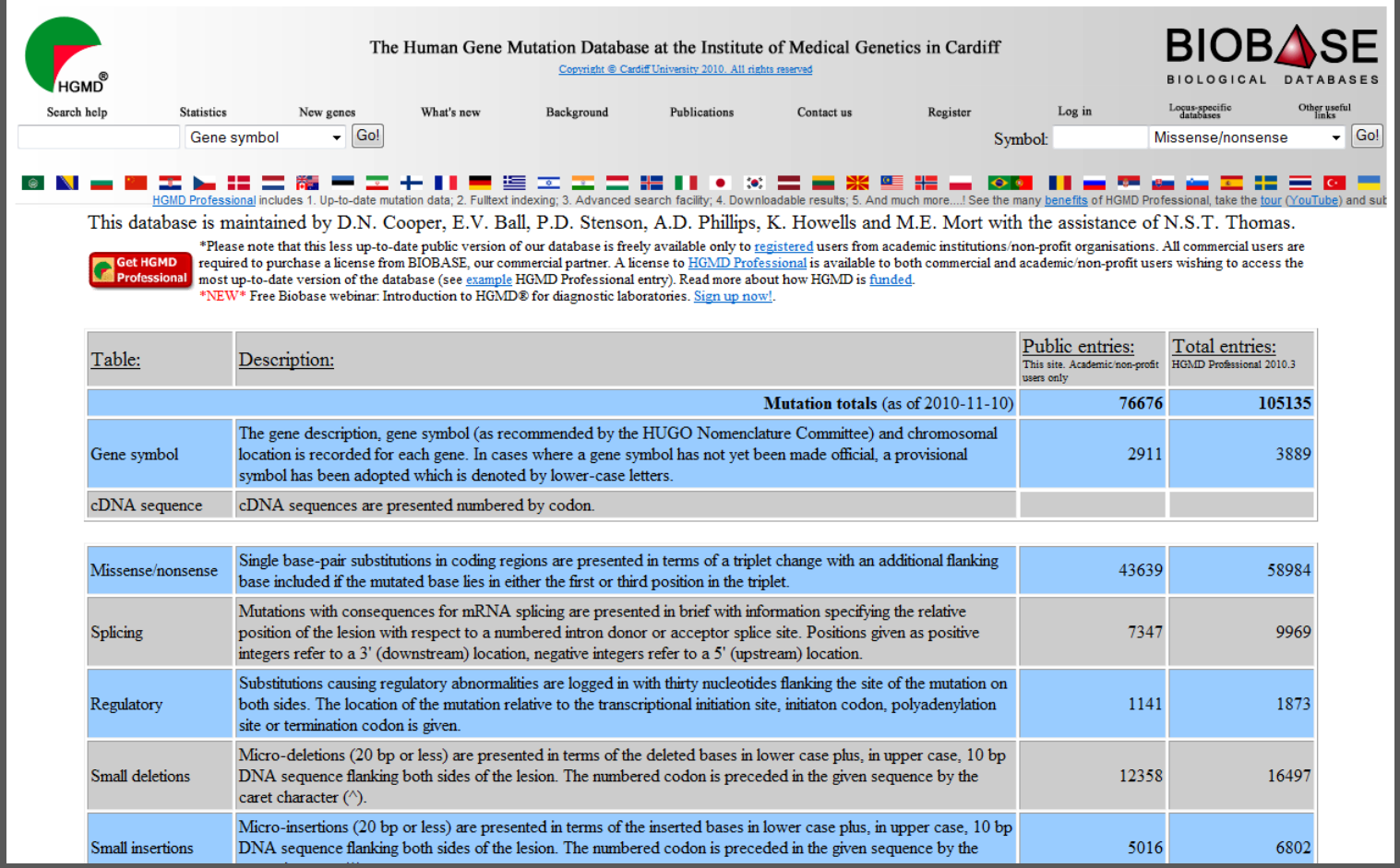




Extracción y análisis del ADN (o ARN)

Acceso a las regiones relevantes del genoma mediante PCR





The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff

HGMD® BIOBASE BIOLOGICAL DATABASES

Search help | Statistics | New genes | What's new | Background | Publications | Contact us | Register | Log in | Locus-specific databases | Other useful links

Gene symbol Go! Symbol: Missense/nonsense Go!

HGMD Professional includes 1. Up-to-date mutation data; 2. Fulltext indexing; 3. Advanced search facility; 4. Downloadable results; 5. And much more....! See the many benefits of HGMD Professional, take the tour (YouTube) and sub

This database is maintained by D.N. Cooper, E.V. Ball, P.D. Stenson, A.D. Phillips, K. Howells and M.E. Mort with the assistance of N.S.T. Thomas.

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Table:	Description:	Public entries: This site. Academic/non-profit users only	Total entries: HGMD Professional 2010.3
	Mutation totals (as of 2010-11-10)	**76676**	**105135**
Gene symbol	The gene description, gene symbol (as recommended by the HUGO Nomenclature Committee) and chromosomal location is recorded for each gene. In cases where a gene symbol has not yet been made official, a provisional symbol has been adopted which is denoted by lower-case letters.	2911	3889
cDNA sequence	cDNA sequences are presented numbered by codon.		
Missense/nonsense	Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional flanking base included if the mutated base lies in either the first or third position in the triplet.	43639	58984
Splicing	Mutations with consequences for mRNA splicing are presented in brief with information specifying the relative position of the lesion with respect to a numbered intron donor or acceptor splice site. Positions given as positive integers refer to a 3' (downstream) location, negative integers refer to a 5' (upstream) location.	7347	9969
Regulatory	Substitutions causing regulatory abnormalities are logged in with thirty nucleotides flanking the site of the mutation on both sides. The location of the mutation relative to the transcriptional initiation site, initiaton codon, polyadenylation site or termination codon is given.	1141	1873
Small deletions	Micro-deletions (20 bp or less) are presented in terms of the deleted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the caret character (^).	12358	16497
Small insertions	Micro-insertions (20 bp or less) are presented in terms of the inserted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the	5016	6802

Comparación frente a las bases de datos de mutaciones

Interpretación biológica de los resultados

Interpretación clínica

Emisión de un informe de utilidad clínica

Comunicación al médico

Comunicación al paciente

Toma de decisiones

Hacia la Medicina Genómica y Medicina Personalizada

Del análisis de genes individuales al análisis del genoma completo

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Perspective

JULY 22, 2010

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic variability in patients' responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other molecular mechanisms to better predict patients' responses to targeted therapy.

The challenge is to deliver the benefits of this work to patients. As the leaders of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), we have a shared vision of personalized medicine and the scientific and regulatory structure needed to support its growth. Together, we have been focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time.

We recognize that myriad obstacles must be overcome to achieve these goals. These include scientific challenges, such as determining which genetic markers have the most clinical significance, limiting the off-target effects of gene-based therapies, and conducting clinical studies to identify genetic variants that are correlated with a drug response. There are also policy challenges, such as finding a level of regulation for genetic tests that both protects patients and encourages innovation. To make progress, the NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for coordinated approval of codeveloped diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available.

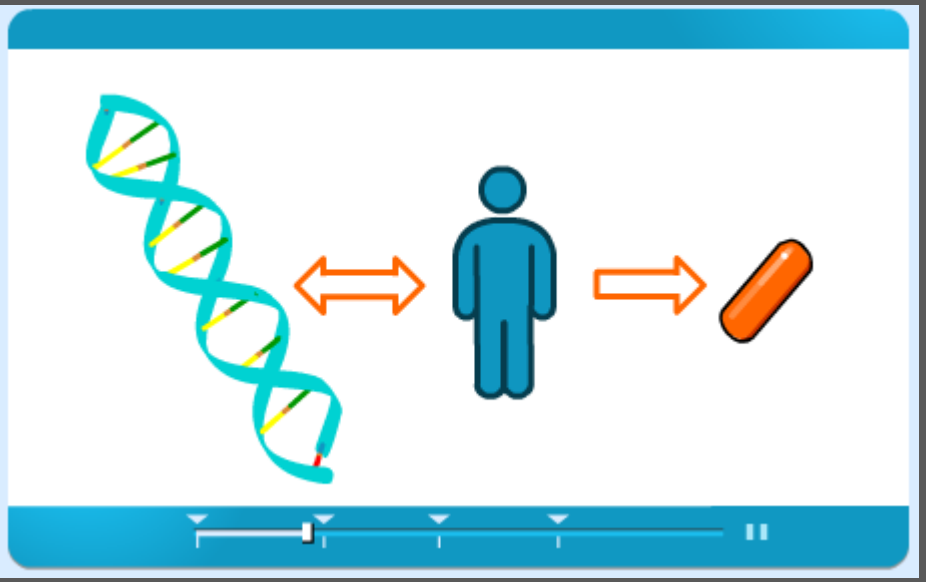
Moving from concept to clinical use requires basic, translational, and regulatory science. On the basic-science front, studies are identifying many genetic variations underlying the risks of both rare and common diseases. These newly discovered genes, proteins, and pathways can represent powerful new drug targets, but currently there is insufficient evidence of a downstream market to entice the private sector to explore most of them. To fill that void, the NIH and the FDA will

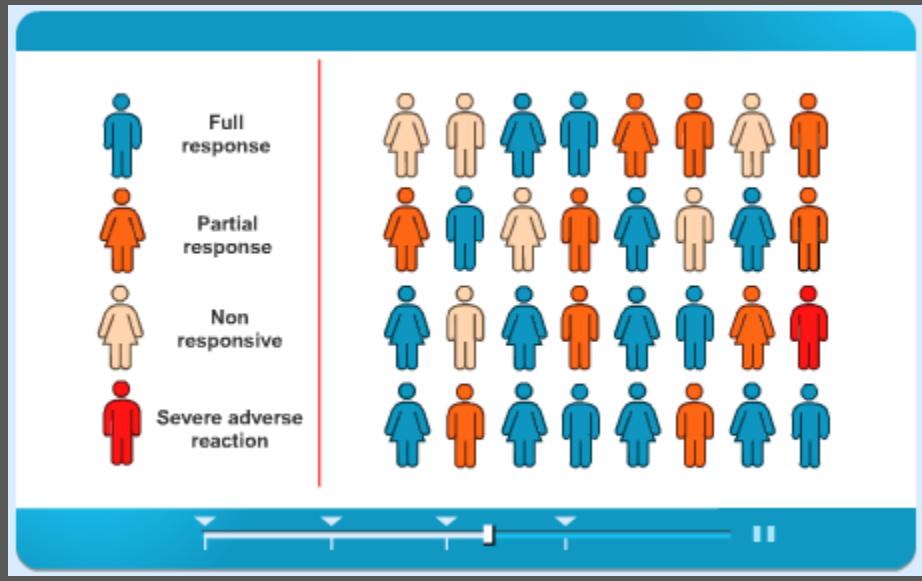
Aplicaciones de la Medicina Genómica

- Genética Médica
- Comprensión de la enfermedad y desarrollo de nuevos fármacos
- Farmacogenómica y farmacogenética
- Genómica personal: tests genéticos directos al consumidor (!)

Farmacogenética y Farmacogenómica

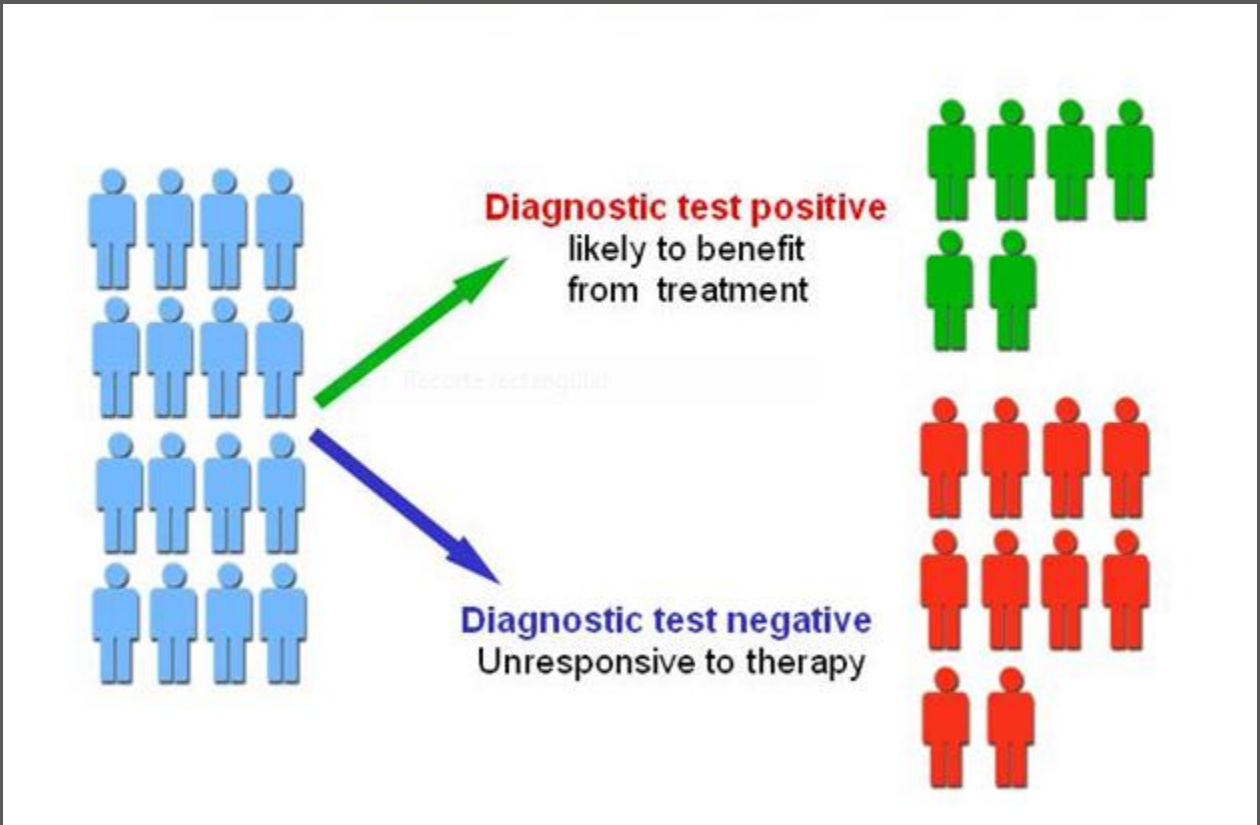
CONCEPTOS BÁSICOS





www.phgfoundation.org/tutorials/pharmacogenomics

Hacia una prescripción individualizada



www.youtube.com/user/PHGFoundation#p/a/DFDD9CFF28132E1F/0/-6TEfYZQZnw

www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Pharmacogenomic Biomarkers in Drug Labels

Drug	Therapeutic Area	Biomarker	Label Sections
Azathioprine	Rheumatology	TPMT	Dosage and Administration, Warnings and Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology
Flurbiprofen	Rheumatology	CYP2C9	Clinical Pharmacology, Special Populations
Clomiphene	Reproductive and Urologic	Rh genotype	Precautions
Tolterodine	Reproductive and Urologic	CYP2D6	Clinical Pharmacology, Drug Interactions, Warnings and Precautions
Drospirenone and Ethinyl Estradiol	Reproductive	CYP2C19	Precautions, Drug Interactions
Tiotropium	Pulmonary	CYP2D6	Clinical Pharmacology
Aripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology
Atomoxetine	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology

www.fda.gov/Training/ForHealthProfessionals/ucm090801.htm

REVIEW ARTICLE

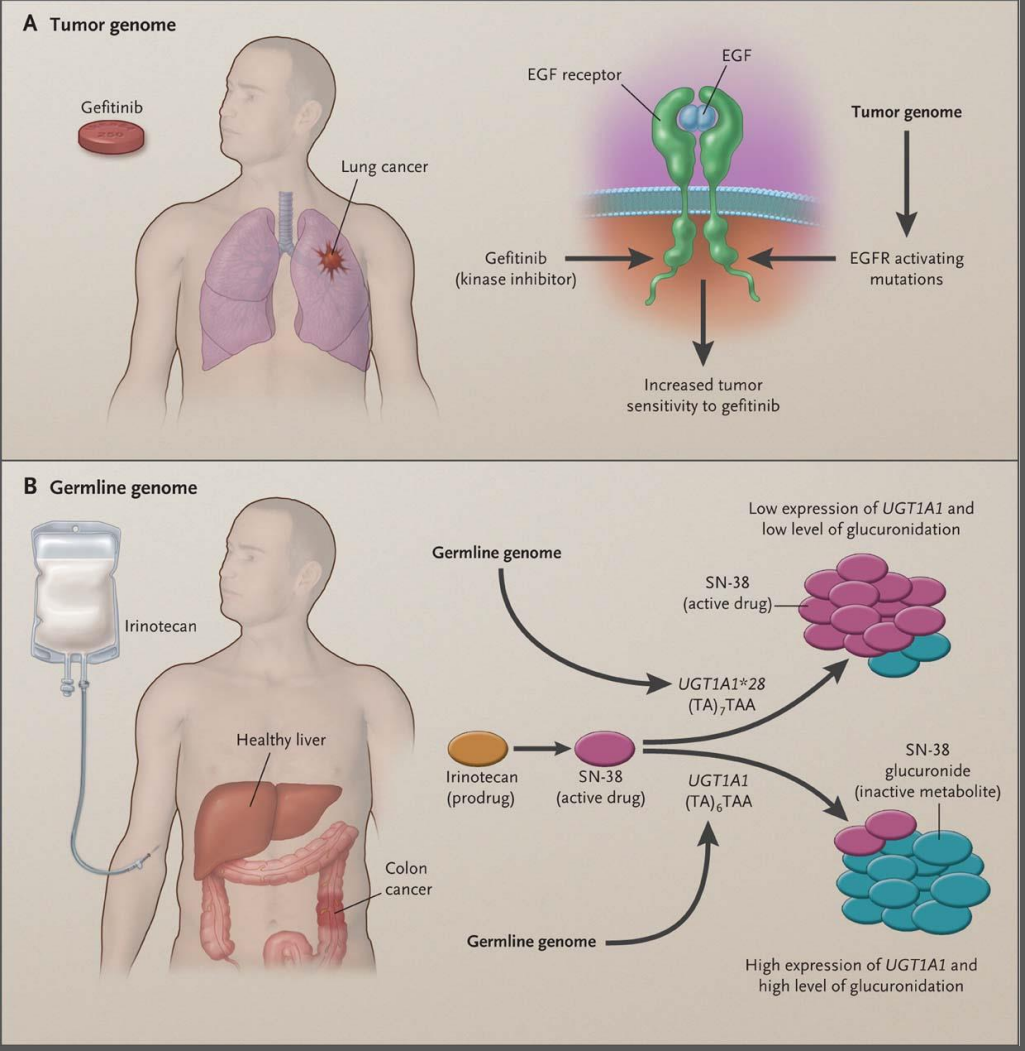
GENOMIC MEDICINE

W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D., *Editors*

Genomics and Drug Response

Liewei Wang, M.D., Ph.D., Howard L. McLeod, Pharm.D.,
and Richard M. Weinshilboum, M.D.

Wang et al (2011). N Engl J Med 364(12): 1144-1153.



The NEW ENGLAND JOURNAL of MEDICINE

Figure 3. Cancer Pharmacogenomics and Tumor and Germline Genomes.

Both the tumor genome (e.g., in the case of gefitinib therapy) and the patient's germline genome (e.g., in the case of irinotecan therapy) can contribute to pharmacogenomic variation in response to antineoplastic drugs. The tumor genome plays a critical role in the response to gefitinib (Panel A), since the sensitivity of non–small-cell lung cancer to this drug is enhanced by activating mutations in the kinase domain of the gene encoding epidermal growth factor receptor (*EGFR*).[58,59] Tumor *EGFR* encoding activating mutations within the kinase domain results in enhanced tumor sensitivity to gefitinib. The rate of toxic effects associated with irinotecan (diarrhea and myelosuppression) is increased in patients with seven TA dinucleotide repeats rather than the more common six repeats in the promoter region of *UGT1A1* encoding a UDP-glucuronosyltransferase in germline DNA, resulting in lower enzyme activity and a decreased rate of drug metabolism (Panel B).[1,62]

Hacia los genomas personales

La secuencia de ADN que salvó al pequeño Nicholas

EE UU usa por primera vez esta técnica para evitar la muerte de un enfermo

DAVID ALANDETE - Washington - 08/01/2011

El pequeño Nicholas Volker, que ahora tiene seis años, estuvo a punto de fallecer en numerosas ocasiones. Sufría no una, sino dos extrañas enfermedades casi imposibles de identificar a través de sus síntomas. Cuando comía, se producían en sus intestinos unos agujeros enormes, por los que las heces se colaban a una herida en su abdomen. Sufría intensos dolores. Desnutrido, en seis meses fue operado en más de 100 ocasiones. En una de ellas le extirparon el colon, recubierto por una misteriosa úlcera amarilla. Vivía así desde los 23 meses, incapaz de comer ni un solo bocado durante la mayor parte de su corta vida.

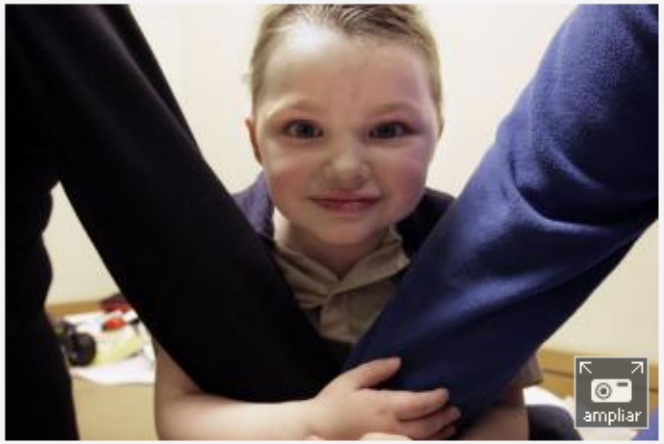
› Menos raras

La noticia en otros webs

webs en español
en otros idiomas

El niño sufre una dolencia que le causa agujeros en el intestino

Los médicos pensaban que su dolencia podía ser la enfermedad de Crohn, que provoca que el sistema inmunitario ataque al intestino del paciente. El tratamiento habitual era, sin embargo, inefectivo sobre Nicholas. En junio de 2009, su pediatra, el doctor Alan Mayer, decidió pedirle a un grupo de especialistas del Centro de Genética Humana y Molecular del Colegio Médico de Wisconsin que analizaran la secuencia genética



Nicholas Volker.- CORTESÍA DE JOURNAL SENTINEL NEWSPAPER AND JOURNAL COMMUNICATIONS INC

ONLINE FIRST

Personalized Medicine vs Guideline-Based Medicine

Jeffrey J. Goldberger, MD, MBA
Alfred E. Buxton, MD

TWO PHILOSOPHICAL APPROACHES TO THE IMPLEMENTation of optimal health care are emerging—the use of evidence-based guidelines and the application of personalized (or "precision") medicine. Even though both approaches have important merits, they both also can present conflicting priorities that must be reconciled before they can be best leveraged.

Evidence-based guidelines are generated based on the body of clinical data available for a particular question. The highest level of evidence assigned in a guideline is based on multiple randomized controlled clinical trials. In general, randomized clinical trials have specific inclusion and exclusion criteria designed to represent a population broad enough and sufficiently enriched to attain a requisite number of end points and demonstrate a statistically and clinically significant difference in outcome. Subgroup analyses (both those that are prespecified and other post hoc analyses) are often performed to identify characteristics within the study population that are associated with greater benefit from the intervention, with no benefit, or even with harm. Yet these analyses are accompanied by warnings that findings should be cautiously interpreted.[1]

Indeed, there is well-deserved skepticism regarding the utility and accuracy of subgroup analysis from clinical trials, and these analyses are therefore generally not used in the formulation of guidelines. Patients (including those enrolled in trials) have multiple characteristics, each of which may influence the behavior and significance of other characteristics. Analysis of a subgroup showing that a single characteristic influences outcome is of limited clinical significance unless multiple variables that may modify the importance of the single variable are considered. However, if well-conducted analyses from multiple sources demonstrate concordant findings, perhaps these subgroup analyses should be considered when guidelines are constructed and revised, given the impracticality of performing randomized clinical trials to answer the question of appropriateness for every possible subgroup.

In the end, "the guidelines" are usually established based on the inclusion criteria for the trial. The applicability of the guidelines may be questioned, or even suspect, when individual patients within the heterogeneous population to which the guidelines are applied in clinical practice differ in certain critical characteristics from those of the trial population on which the guideline recommendation is based. That is, the generalizability of trial results to clinical practice may be compromised by a number of factors involved in execution of the trial, such as where patients were recruited (eg, inpatient vs outpatient venue, tertiary referral centers vs primary care centers).

The President's Council of Advisors on Science and Technology noted that personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."[2] Although the increasing attention directed to personalized medicine has largely focused on the interaction of an individual's genome with specific treatments, any individual characteristics that affect treatment outcomes may be relevant to clinical decision making. If certain subpopulations within the total cohort of a clinical trial were considered unlikely to benefit from the intervention—based, for example, on actual subgroup analysis—this hypothesis would need to be tested prospectively in a separate clinical trial to achieve a sufficient level of evidence about the value of the intervention in this patient subpopulation.

Although it is possible to make a case for equipoise in such a situation, once the guidelines include this subpopulation in the general group in which the intervention is recommended based on the results (or entry criteria) of clinical trials, it is difficult to overcome the multidimensional resistance to actually testing "not providing the intervention" when the guidelines recommend otherwise. Thus, the development of evidence-based guidelines based on a relatively broad set of enrollment criteria inhibits the subsequent development of personalized medicine within this "enrollment criteria" space.

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Next Generation Sequencing - NGS

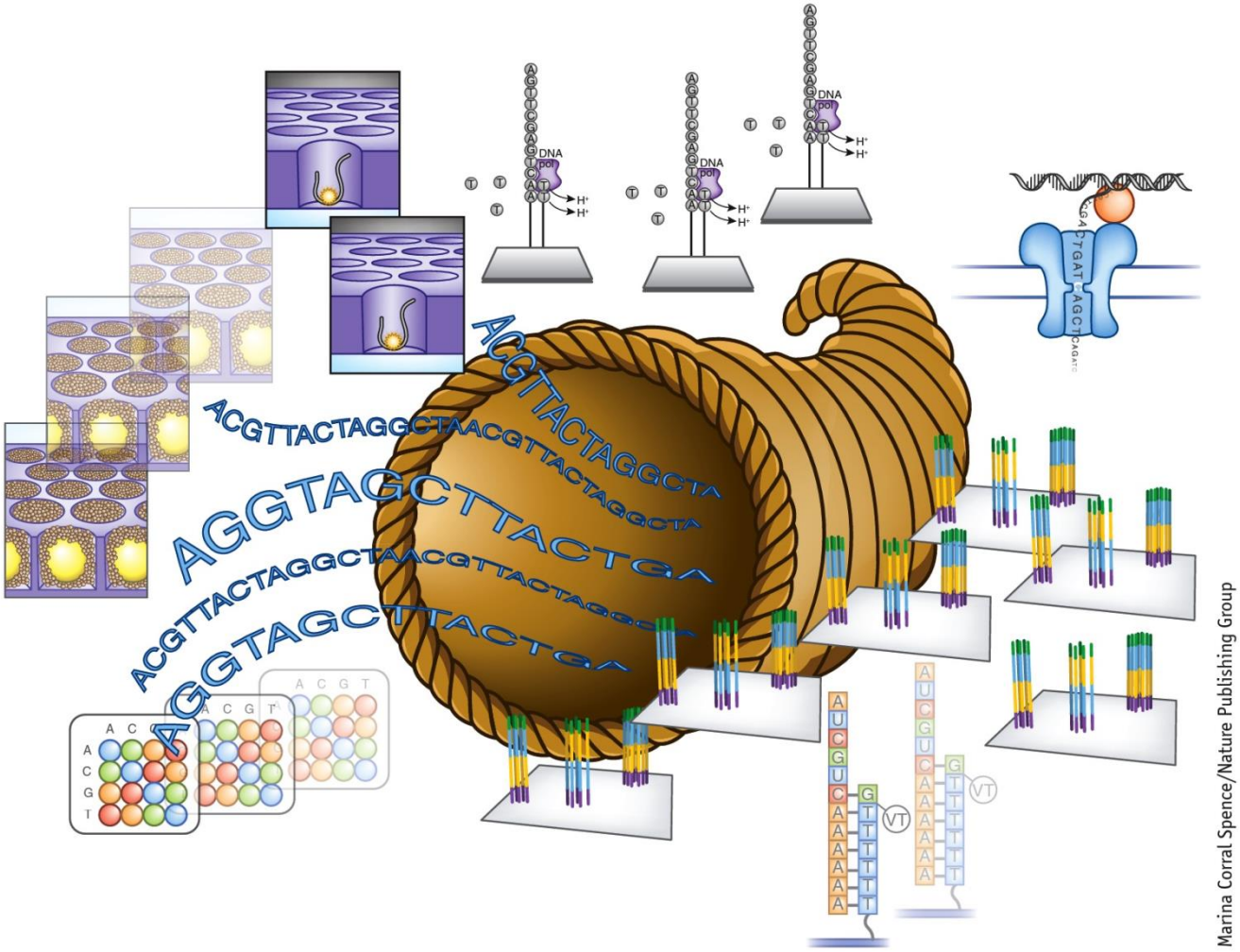


Figure 1 | Sequencing technologies are evolving, with many platforms now reaching maturity as a few others have failed or are being phased out. The future face of sequencing is unclear, but a bountiful sequencing capacity is assured for the future.

Mc Pherson (2014). A defining decade in DNA Sequencing. **Nature Methods**. Octubre 2014

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Elizabeth G. Phimister, Ph.D., *Editor*

Diagnostic Clinical Genome and Exome Sequencing

Leslie G. Biesecker, M.D., and Robert C. Green, M.D., M.P.H.

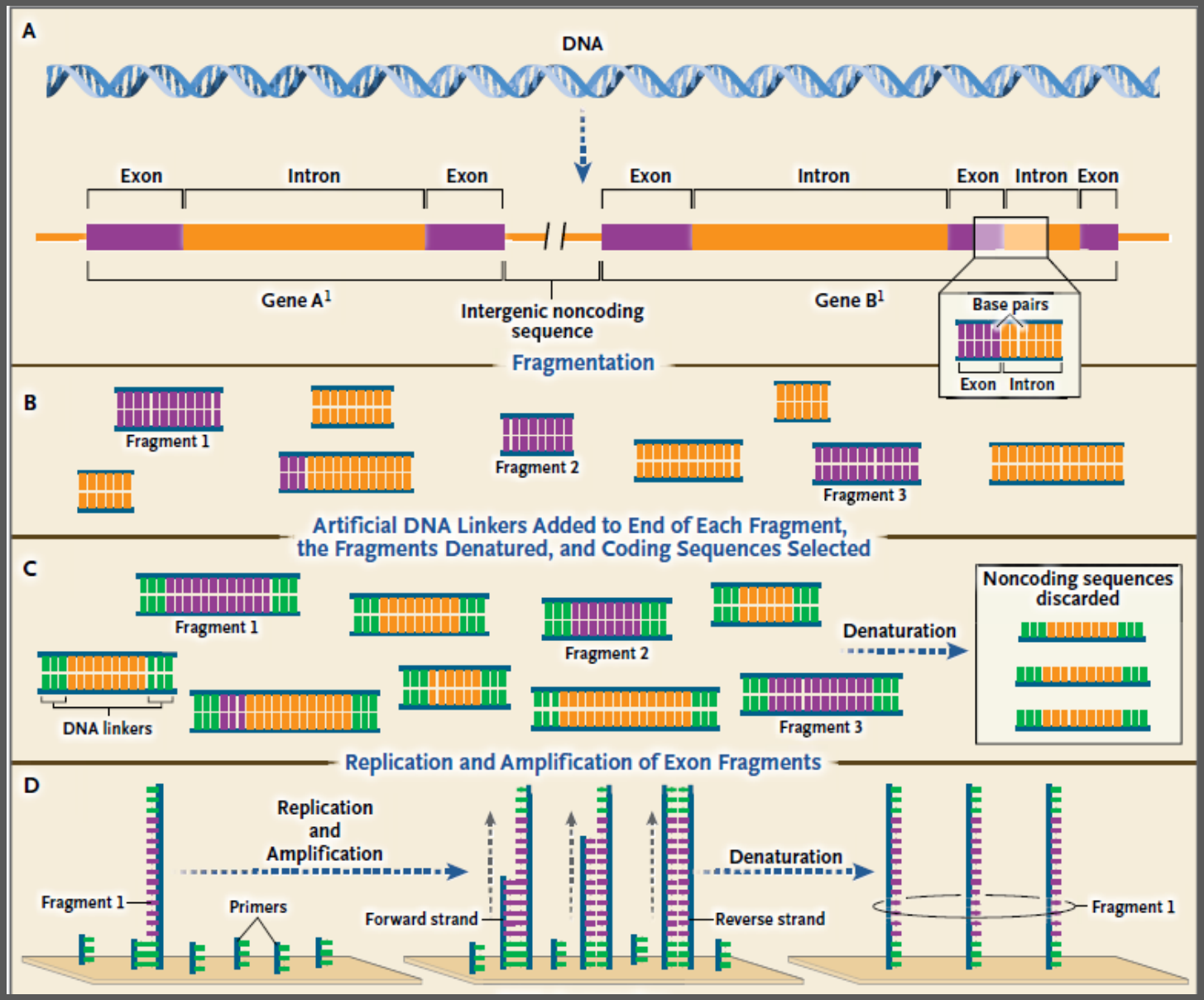
SEQUENCING OF THE GENOME OR EXOME FOR CLINICAL APPLICATIONS, hereafter referred to as clinical genome and exome sequencing (CGES), has now entered medical practice.[1] Several thousand CGES tests have already been ordered for patients, with the goal of establishing diagnoses for rare, clinically unrecognizable, or puzzling disorders that are suspected to be genetic in origin. We anticipate increases in the use of CGES, the key attribute of which — its breadth — distinguishes it from other forms of laboratory testing. The interrogation of variation in about 20,000 genes simultaneously can be a powerful and effective diagnostic method.[2]

CGES has been hailed as an important tool in the implementation of predictive and individualized medicine, and there is intense research interest in the clinical benefits and risks of sequencing for screening healthy persons[3]; however, current practice recommendations[4] do not support the use of sequencing for this purpose, and for that reason we do not further address it here. We have also limited this overview of CGES to the analysis of germline sequence variants for diagnostic purposes and do not discuss the use of CGES to uncover somatic variants in cancer in order to individualize cancer therapy.

Clinicians should understand the diagnostic indications for CGES so that they can effectively deploy it in their practices. Because the success rate of CGES for the identification of a causative variant is approximately 25%,[5] it is important to understand the basis of this testing and how to select the patients most likely to benefit from it. Here, we summarize the technologies underlying CGES and offer our insights into how clinicians should order such testing, interpret the results, and communicate the results to their patients (an interactive graphic giving an overview of the process is available with the full text of this article at NEJM.org).

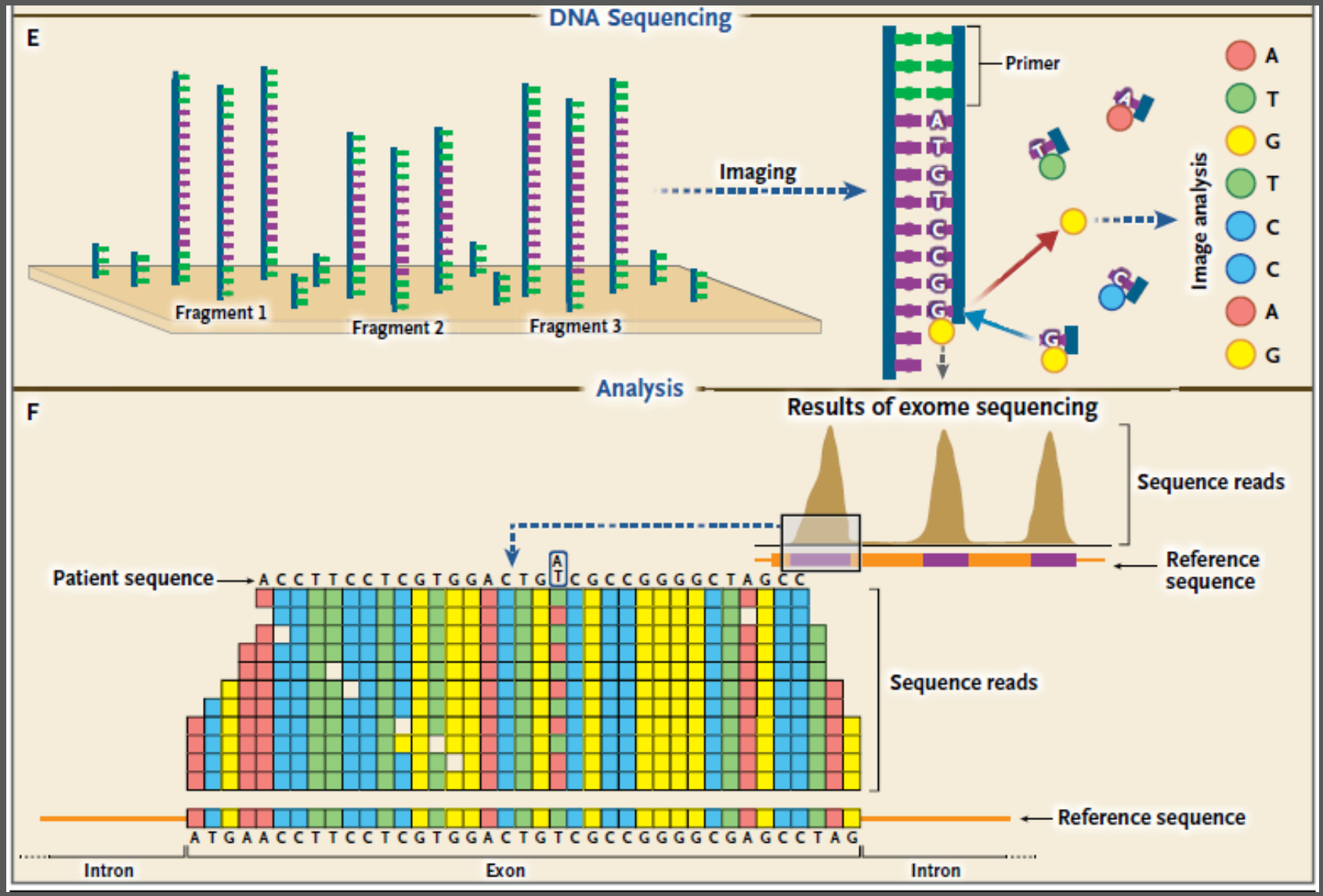
NEJM. Junio 2014

SECUENCIACIÓN DE EXOMAS (1)



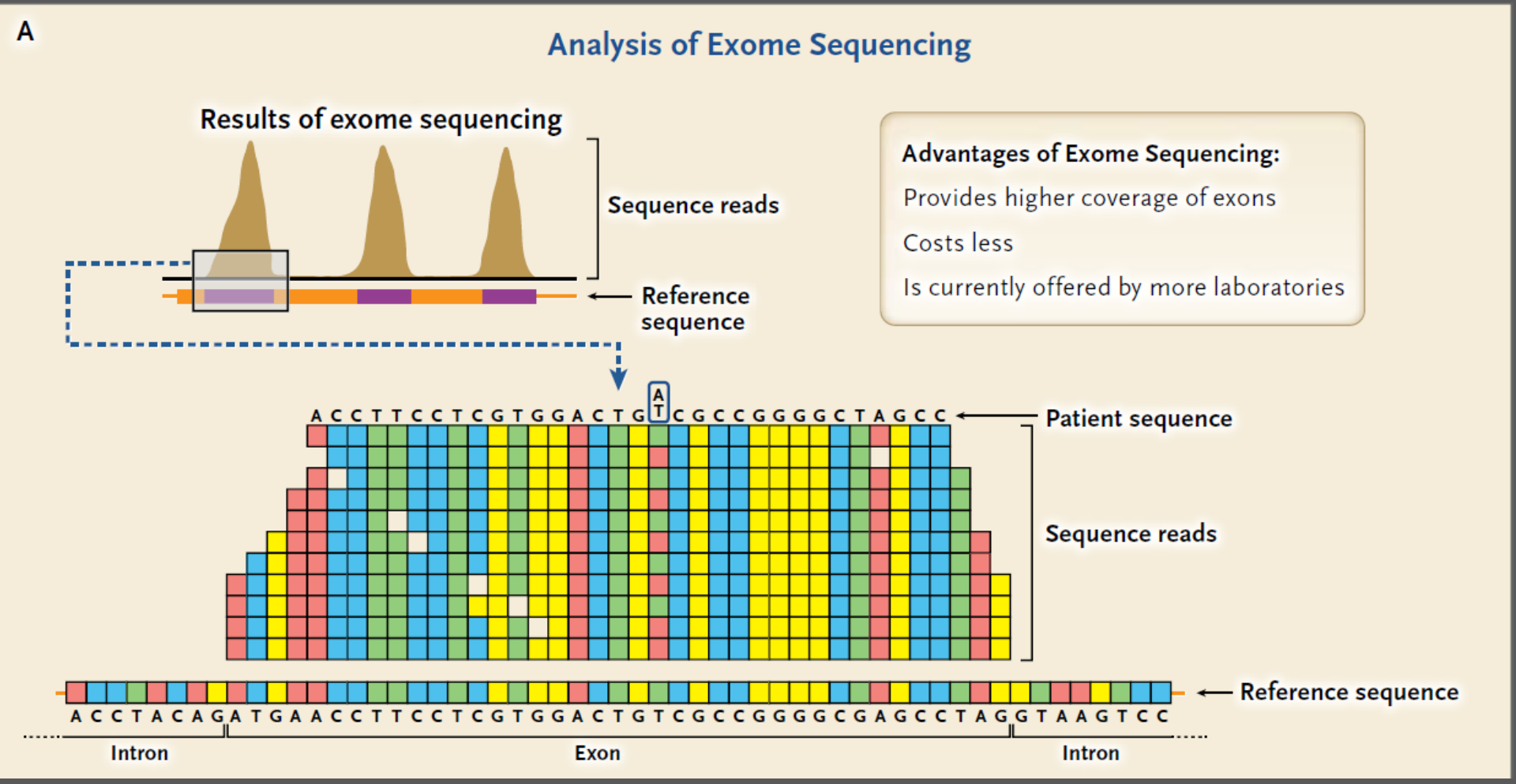
Biesecker et al (2014). Diagnostic Clinical Genome and Exome Sequencing. **NEJM**. Junio.

SECUENCIACIÓN DE EXOMAS (2)



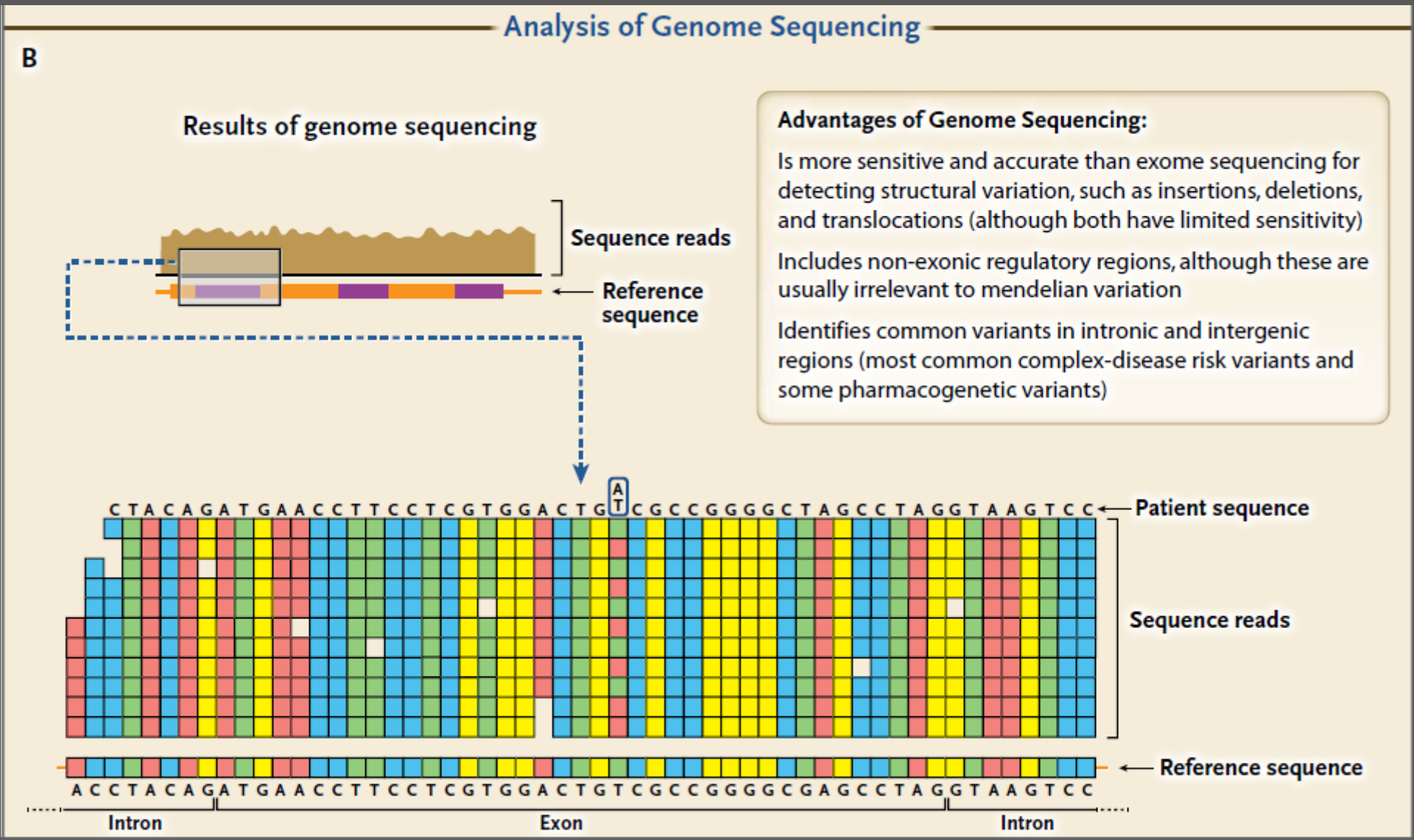
Biesecker et al (2014). Diagnostic Clinical Genome and Exome Sequencing. **NEJM**. Junio.

SECUENCIACIÓN DE EXOMAS (3)



Biesecker et al (2014). Diagnostic Clinical Genome and Exome Sequencing. **NEJM**. Junio.

EXOMA vs GENOMA COMPLETO



Biesecker et al (2014). Diagnostic Clinical Genome and Exome Sequencing. **NEJM**. Junio.

with information representing the number of sequence reads generated (depth of coverage) and the accuracy of the genotype at each position. The output file is computationally filtered in accordance with the clinical objective of the test and the preferences of the laboratory. Typically, the file is filtered for variants that are rare or have not previously been reported (because it is reasoned that a common variant cannot cause a rare disease), variants predicted to cause a loss or altered function of a gene, and variants previously reported to cause disease.[10,11]

CGES is most useful for the detection of single-nucleotide substitutions and insertions or deletions of 8 to 10 nucleotides or smaller; it is less accurate for other types of genomic variation (Table 1). The yield of sequence reads is inherently uneven across the exome (or genome) — typical results provide adequate coverage of 85 to 95% of the targeted sequence. With exome sequencing, there is also variable coverage of flanking intronic regions, which may include disease-causing variants that affect the splicing of messenger RNA encoded by the gene (splice variants).

Glossary

Exome sequencing: DNA sequencing that targets the exons of all genes in the genome. The exome makes up about 1% of the genome, primarily exons of genes that code for proteins. This type of sequencing is sometimes referred to as "whole-exome sequencing," even though coverage of the exons is not 100%.

Exons: Segments of genes that are spliced together after gene transcription to form messenger RNA, which, in turn, is translated into protein.

Expressivity: Variation in the severity of a genetic disorder among persons with some features of the condition.

Filtering analysis: The process of excluding DNA variants from further consideration because of various attributes, with the use of bioinformatics and manual curation. For example, most filtering analyses exclude synonymous variants (DNA variants that are predicted not to change the amino acid sequence of a protein).

Genome sequencing: DNA sequencing that targets the entire genome. It is sometimes termed "genome shotgun sequencing" or "whole-genome sequencing," even though coverage is not 100%.

Germline variant: A DNA sequence variant that was transmitted by means of a gamete (sperm or egg) or that was caused by a mutation in the zygote or at a very early stage of fetal development and is presumed to be present in all of a person's nucleated cells.

Human genome reference sequence: A reference sequence that provides a haploid mosaic of different DNA sequences from multiple donors, which is revised periodically and is not necessarily normal.

Penetrance: The likelihood that a person with a causative variant in a gene has any recognizable symptom, sign, or laboratory feature of the disease associated with that variant.

Sanger sequencing: A method of sequence determination, invented by Frederick Sanger, that uses dideoxy terminator nucleotide chemistry, with the reaction products separated by gel electrophoresis.

Variant: A difference in a DNA sequence in comparison with the normal reference sequence. A variant may be benign (sometimes referred to as a polymorphism) or pathogenic (sometimes referred to as a mutation).

INDICATIONS FOR ORDERING CGES

CGES is currently indicated for the detection of rare variants in patients with a phenotype suspected to be due to a mendelian (single-gene) genetic disorder, after known single-gene candidates have been eliminated from consideration or when a multigene testing approach is prohibitively expensive. Patients can be of any age but are commonly children, since many genetic conditions are manifested in childhood; evaluations are performed because parents are searching for the cause or for information to guide management and treatment and desire accurate information regarding the risk of recurrence, as noted below.

The preparation for ordering CGES should include four key elements: gathering information about the patient's personal and family history, including other potentially relevant manifestations. For

and phenotypes.[14] In the literature, however, there are many false attributions of disease to variants, a problem that is in part due to the conflation of association with causation.[15] Clinicians reviewing the results of sequencing should be aware of the possibility of a false attribution of pathogenicity to a variant[16] and should realize that the chances of false attribution are increased in CGES because thousands of genes are tested simultaneously.

The clinical usefulness of identifying the variant that is the cause of a previously undiagnosed syndrome or heritable disorder varies. In some cases, it can lead to a specific treatment or management strategy that dramatically changes the clinical outcome.[17,18] In the majority of cases in which the finding does not change clinical management, treatment, or prognosis, it may still be useful because it can end an expensive, potentially invasive, and stressful diagnostic odyssey. The identification of the causative variant may provide accurate estimates of recurrence risk and facilitate preconception intervention or prenatal diagnosis for the affected patient or affected or at-risk relatives. In adult-onset disease, one of the most useful outcomes of successfully identifying the causative variant is the subsequent detection of presymptomatic, at-risk siblings for whom screening or preventive therapy might improve the clinical outcome. Examples include enhanced surveillance or prophylactic surgery for patients found to have a genetic susceptibility to cancer.

Pretest counseling is particularly important, to maintain realistic expectations for finding the causative variant and to alert the patient or family that in most cases, a positive result is unlikely to change treatment or management decisions or to improve the prognosis.[19] In addition, the patient should be advised that incidental findings unrelated to the reason for testing may be found and reported, as described below. It may also be important to discuss the cost of the test with the patient. As is the case with many medical services, assessment of the cost is complicated by many factors. The published billing charge for CGES in most laboratories is in the range of $4,000 to $15,000 per patient, with

Table 2. Examples of Online Databases to Assist Clinicians in Differential Diagnosis or Candidate-Gene Identification for Rare Syndromic Disorders before CGES Is Performed.

Free access (or an available free-access version)
Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr)
HuGE Navigator (http://hugenavigator.net/HuGENavigator)
Human Gene Mutation Database (www.biobase-international.com/product/hgmd)
Online Mendelian Inheritance in Man (www.omim.org)
Phenomizer (http://compbio.charite.de/phenomizer)
SimulConsult (www.simulconsult.com)
Subscription or fee required for access
Isabel (www.isabelhealthcare.com/home/default)
London Medical Databases (http://lmdatabases.com)
POSSUM (www.possum.net.au)

published billing charge for some single-gene sequencing tests, which is why exome sequencing can be more efficient in a number of clinical scenarios. Some laboratories have reported that third-party payers are reimbursing for this testing, but practices vary widely, and patients should understand this in advance.

INTERPRETING AND COMMUNICATING CGES RESULTS

Clinicians should review the CGES results delivered by the laboratory geneticist and place the findings into context with other relevant medical considerations. Sometimes an identified variant will spur additional history taking or an additional examination of the patient, which may reveal clinical features of a previously unrecognized syndrome or lead to the conclusion that the variant is not related to the disorder in the patient (Table 4).

In some cases, the CGES report from the testing laboratory identifies a causative variant (or two variants for a recessive disorder) in a single gene that is considered sufficiently pathogenic and specific that a diagnostic association with a heritable disorder is strongly supported. Such a conclusion by the laboratory geneticist is typi-

Biesecker et al (2014). Diagnostic Clinical Genome and Exome Sequencing. **NEJM**. Junio.

REVIEW | Genetics inMedicine

Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing

Yuan Xue, PhD, FACMG[1], Arunkanth Ankala, PhD[1], William R. Wilcox, MD, PhD[2] and Madhuri R. Hegde, PhD, FACMG[1]

Next-generation sequencing is changing the paradigm of clinical genetic testing. Today there are numerous molecular tests available, including single-gene tests, gene panels, and exome sequencing or genome sequencing. As a result, ordering physicians face the conundrum of selecting the best diagnostic tool for their patients with genetic conditions. Single-gene testing is often most appropriate for conditions with distinctive clinical features and minimal locus heterogeneity. Next-generation sequencing–based gene panel testing, which can be complemented with array comparative genomic hybridization and other ancillary methods, provides a comprehensive and feasible approach for heterogeneous disorders. Exome sequencing and genome sequencing have the advantage of being unbiased regarding what set of genes is analyzed, enabling parallel interrogation of most of the genes in the human genome. However, current limitations of next-generation sequencing technology and our variant interpretation capabilities caution us against offering exome sequencing or genome sequencing as either stand-alone or first-choice diagnostic approaches. A growing interest in personalized medicine calls for the application of genome sequencing in clinical diagnostics, but major challenges must be addressed before its full potential can be realized. Here, we propose a testing algorithm to help clinicians opt for the most appropriate molecular diagnostic tool for each scenario.

Genet Med advance online publication 18 September 2014

Key Words: exome sequencing; gene panel; molecular diagnostic testing; next-generation sequencing; single-gene test

INTRODUCTION

Next-generation sequencing (NGS) technology has been rapidly adapted to clinical testing and is radically changing the paradigm of clinical diagnostics. In some cases, the technology helps end the lengthy search for a genetic cause, referred to as the "diagnostic odyssey." These changes are apparent from the rapid increase in the number of laboratories offering NGS-based tests, the variety of diseases for which the tests are being offered, and the number of such tests being ordered by clinicians. As of April 2014, the Genetic Testing Registry listed more than 450 disease-targeted clinical NGS panels comprising multiple genes available in both the commercial sector and academically affiliated clinical laboratories. Currently, there are approximately 10 clinical laboratories that offer exome sequencing (ES); genome sequencing (GS) is also available from a handful of laboratories.

NGS technology has the appeal of reducing the time and cost of testing, especially when the sequencing involves a larger number of genes, but is it the best diagnostic tool in all clinical scenarios? Does targeted single-gene analysis still have a place? For gene panels, is including more genes always better? Why choose gene panel testing when ES can give information about all coding regions and is becoming more widely available? ES may even have become the first-tier test to screen for genetic causes for some ordering physicians. The question of what role the clinician plays in performing a detailed clinical assessment of the patient in order to choose the best diagnostic tool is raised. Therefore, a comprehensive overview comparing the different testing approaches and outlining the indications for each test type is urgently needed. In this review, we evaluate these genetic testing options in terms of clinical indications, challenges in the interpretation and reporting of sequencing variants, and technical strengths and limitations. We also propose a testing algorithm that may help ordering physicians opt for the most appropriate molecular diagnostic tool for each scenario.

INDICATIONS FOR SINGLE-GENE, GENE PANEL, AND ES TESTING

The power of NGS-based tests has been demonstrated in many cases. One extreme example is a 50-hour GS offered at neonatal intensive care units that identified a genetic diagnosis in two children.[1] However, it is critical to note that the traditional approach (e.g., single-gene testing and methylation analysis) still holds great value for many disorders. In a retrospective

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¿Qué test genético es el indicado en nuestro caso clínico?

Table 1 Indications for single-gene, gene panel, and ES tests

Testing option	Indications	Examples	Reference
Single-gene test	Minimal locus heterogeneity	*CFTR* for CF	32
	Distinctive clinical findings (e.g., X-ray, biochemical evaluation) clearly point to a specific gene	*FGFR3* for achondroplasia; *PAH* for PKU	4,33
	Limitations of NGS sequencing technology to detect trinucleotide repeat disorders and disorders with epigenetic abnormalities	Fragile X; Prader-Willi and Angleman syndrome	34,35
Gene panel	Heterogeneity	Muscular dystrophies panel	16
	Disorders with overlapping phenotype—differential diagnosis	Cardiomyopathy panel	36
	Disorders share one manifestation but may have completely different overall presentation	Epilepsy panel	37
	Diseases associated with genes from a common pathway or structure	RASopathies panel	38
ES/GS[a]	Extreme heterogeneity and de novo changes are the major mutations	Autism, ID	39
	Two or more likely unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia	40
	No key phenotypic feature is present at the time when the test is ordered	Kabuki syndrome	41
	Phenotype is indistinct, and the real underlying cause is not easy to identify	Congenital diarrhea; Zellweger syndrome	42,43

CDG, congenital disorder of glycosylation; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ES, exome sequencing; FGFR3, fibroblast growth factor receptor 3; GS, genome sequencing; ID, intellectual disability; NGS, next-generation sequencing; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; RASopathies, a group of genetic disorders caused by pathogenic variants in genes that encode components of the Ras/mitogen-activated protein kinase (MAPK) pathway.

[a]ES/GS selection is based on cost and ability to performance analysis. GS is typically performed at a lower depth than ES; the cost of performing the assay, performing analysis, and storage is more than that for ES.

Xue et al (2014). **Genetics in Medicine**. Septiembre

¿Qué test genético es el indicado?

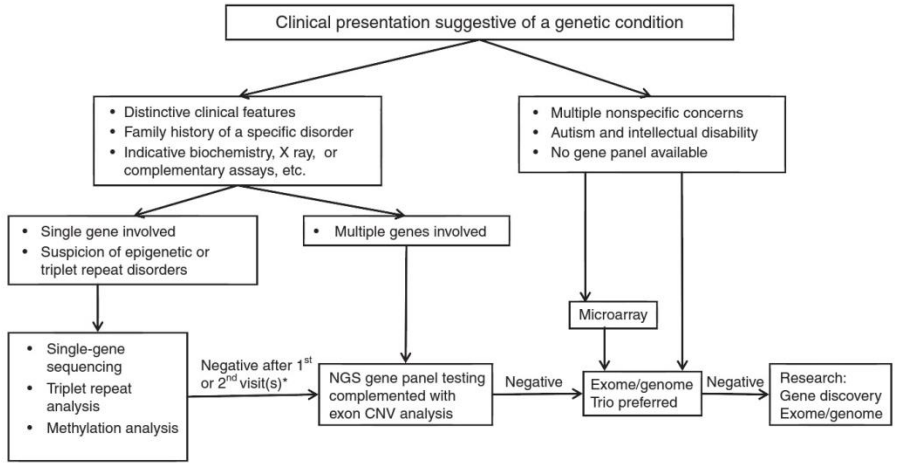

Figure 1 Molecular genetic testing algorithm. *This suggestion is based on the study by Shashi et al.[2]

Table 2 Comparison between single-gene, gene panel, and ES tests

	Single-gene test	Gene panel	Exome sequencing
Phenotype level	Specific features point to one disorder associated with one gene	Genetically heterogeneous disorders	Multiple nonspecific features; extreme heterogeneity (e.g., ID)
Gene level	Disease-causing genes	Well-defined disease-associated genes	All 20,000 genes with 4,600 medically well-defined genes
Variant level	Minimal VUS	Fewer VUS than exome sequencing	Large number of VUS
	No IFs	Less likely to find IFs	Potential to find IFs
Technical issues	Traditional Sanger: gold standard for sequencing	Need Sanger confirmation	Need Sanger confirmation
		Overall higher coverage than exome sequencing	Coverage is compromised
		Sanger fill in for 100% coverage; complementary assays such as targeted gene arrays to detect deletions/duplications	No Sanger fill in

ID, intellectual disability; IF, incidental finding; NGS, next-generation sequencing; VUS, variants of unknown significance.

Xue et al (2014). **Genetics in Medicine**. Septiembre

ORIGINAL ARTICLE

Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D., Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S., Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D., Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D., Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D., Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D., James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D., Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.

ABSTRACT

BACKGROUND

Whole-exome sequencing is a diagnostic approach for the identification of molecular defects in patients with suspected genetic disorders.

METHODS

We developed technical, bioinformatic, interpretive, and validation pipelines for whole-exome sequencing in a certified clinical laboratory to identify sequence variants underlying disease phenotypes in patients.

RESULTS

We present data on the first 250 probands for whom referring physicians ordered whole-exome sequencing. Patients presented with a range of phenotypes suggesting potential genetic causes. Approximately 80% were children with neurologic phenotypes. Insurance coverage was similar to that for established genetic tests. We identified 86 mutated alleles that were highly likely to be causative in 62 of the 250 patients, achieving a 25% molecular diagnostic rate (95% confidence interval, 20 to 31). Among the 62 patients, 33 had autosomal dominant disease, 16 had autosomal recessive disease, and 9 had X-linked disease. A total of 4 probands received two nonoverlapping molecular diagnoses, which potentially challenged the clinical diagnosis that had been made on the basis of history and physical examination. A total of 83% of the autosomal dominant mutant alleles and 40% of the X-linked mutant alleles occurred de novo. Recurrent clinical phenotypes occurred in patients with mutations that were highly likely to be causative in the same genes and in different genes responsible for genetically heterogeneous disorders.

CONCLUSIONS

Whole-exome sequencing identified the underlying genetic defect in 25% of consecutive patients referred for evaluation of a possible genetic condition. (Funded by the National Human Genome Research Institute.)

From the Departments of Molecular and Human Genetics (Y.Y., A.W., P.A.W., A.B., J.B., F.X., Z.N., M.H., R.P., M.R.B., M.S.L., A.K., J.S., S.E.P., J.R.L., A.L.B., C.M.E.) and Pediatrics (S.E.P., J.R.L.) and the Human Genome Sequencing Center (D.M.M., J.G.R., M.N.B., P.P., M.W., Y.D., J.R.L., R.A.G.), Baylor College of Medicine, Houston. Address reprint requests to Dr. Eng at the Department of Molecular and Human Genetics, NAB 2015, Baylor College of Medicine, Houston, TX 77030, or at ceng@bcm.edu.

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Original Investigation

Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing

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IMPORTANCE Clinical whole-exome sequencing is increasingly used for diagnostic evaluation of patients with suspected genetic disorders.

OBJECTIVE To perform clinical whole-exome sequencing and report (1) the rate of molecular diagnosis among phenotypic groups, (2) the spectrum of genetic alterations contributing to disease, and (3) the prevalence of medically actionable incidental findings such as *FBN1* mutations causing Marfan syndrome.

DESIGN, SETTING, AND PATIENTS Observational study of 2000 consecutive patients with clinical whole-exome sequencing analyzed between June 2012 and August 2014. Whole-exome sequencing tests were performed at a clinical genetics laboratory in the United States. Results were reported by clinical molecular geneticists certified by the American Board of Medical Genetics and Genomics. Tests were ordered by the patient's physician. The patients were primarily pediatric (1756 [88%]; mean age, 6 years; 888 females [44%], 1101 males [55%], and 11 fetuses [1% gender unknown]), demonstrating diverse clinical manifestations most often including nervous system dysfunction such as developmental delay.

MAIN OUTCOMES AND MEASURES Whole-exome sequencing diagnosis rate overall and by phenotypic category, mode of inheritance, spectrum of genetic events, and reporting of incidental findings.

RESULTS A molecular diagnosis was reported for 504 patients (25.2%) with 58% of the diagnostic mutations not previously reported. Molecular diagnosis rates for each phenotypic category were 143/526 (27.2%; 95% CI, 23.5%-31.2%) for the neurological group, 282/1147 (24.6%; 95% CI, 22.1%-27.2%) for the neurological plus other organ systems group, 30/83 (36.1%; 95% CI, 26.1%-47.5%) for the specific neurological group, and 49/244 (20.1%; 95% CI, 15.6%-25.8%) for the nonneurological group. The Mendelian disease patterns of the 527 molecular diagnoses included 280 (53.1%) autosomal dominant, 181 (34.3%) autosomal recessive (including 5 with uniparental disomy), 65 (12.3%) X-linked, and 1 (0.2%) mitochondrial. Of 504 patients with a molecular diagnosis, 23 (4.6%) had blended phenotypes resulting from 2 single gene defects. About 30% of the positive cases harbored mutations in disease genes reported since 2011. There were 95 medically actionable incidental findings in genes unrelated to the phenotype but with immediate implications for management in 92 patients (4.6%), including 59 patients (3%) with mutations in genes recommended for reporting by the American College of Medical Genetics and Genomics.

CONCLUSIONS AND RELEVANCE Whole-exome sequencing provided a potential molecular diagnosis for 25% of a large cohort of patients referred for evaluation of suspected genetic conditions, including detection of rare genetic events and new mutations contributing to disease. The yield of whole-exome sequencing may offer advantages over traditional molecular diagnostic approaches in certain patients.

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Editorial
Related article
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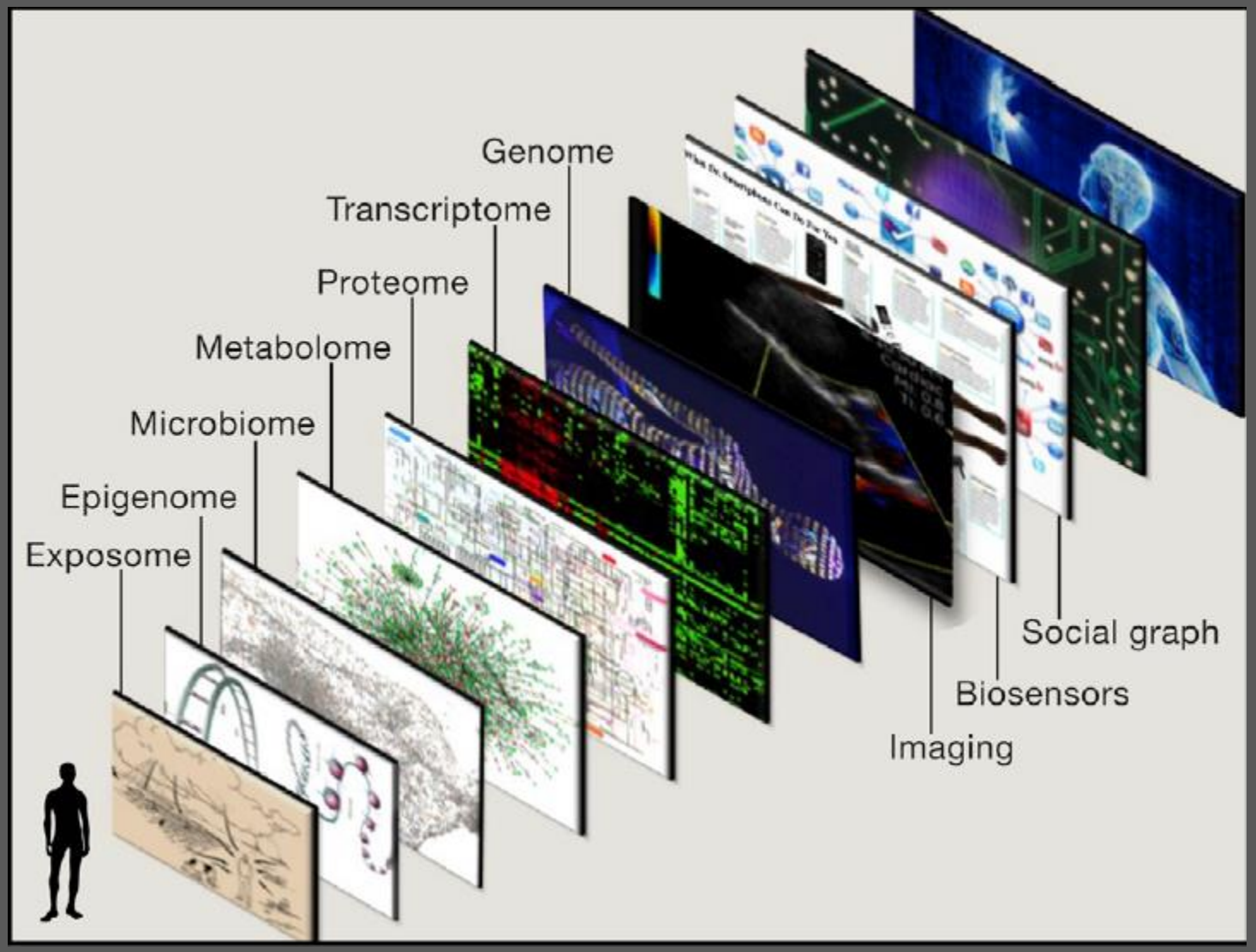
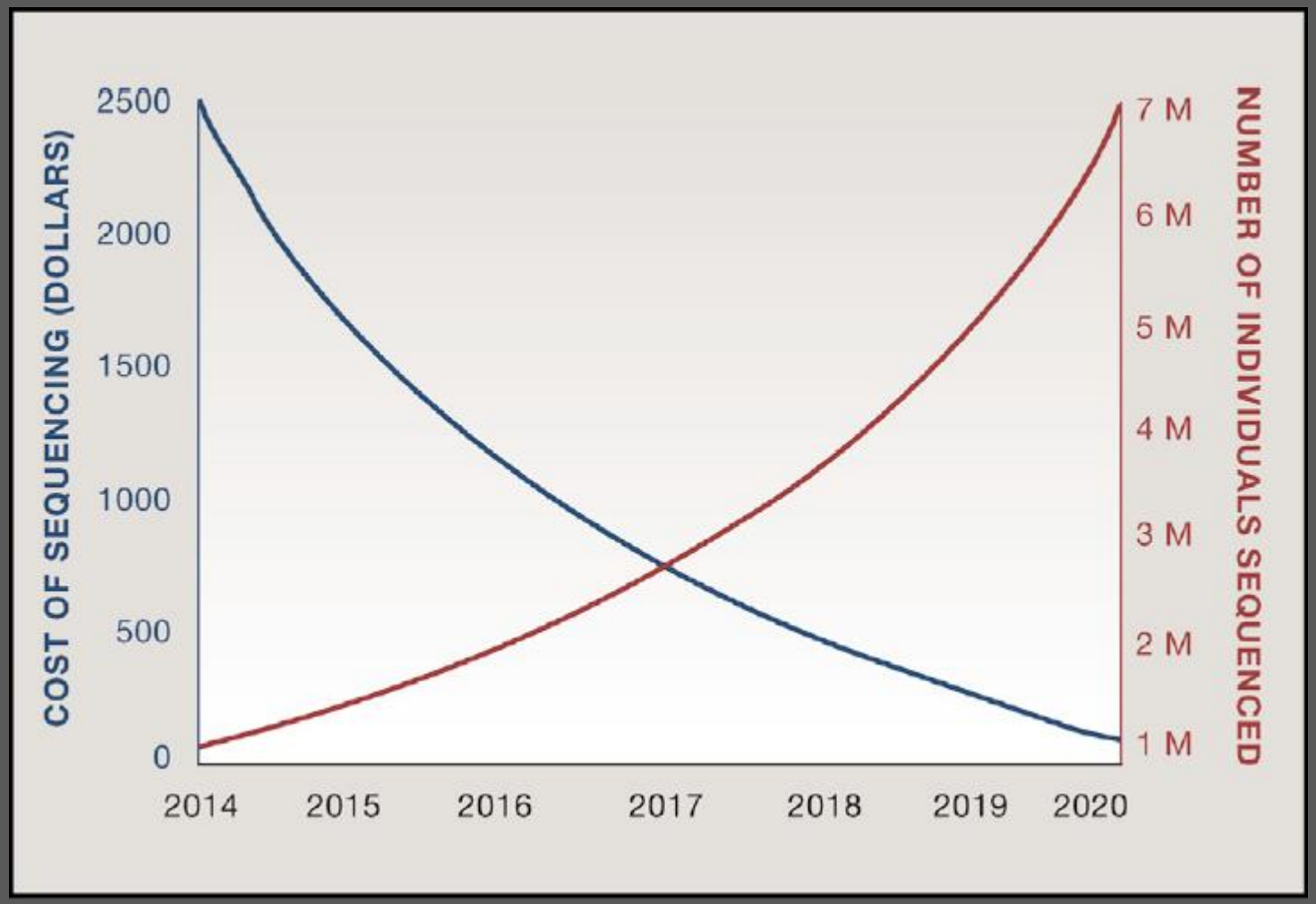
Corresponding Author: Christine M. Eng, MD, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 (ceng@bcm.edu).

Tendencias (1)



Topol (2014). Individualized Medicine from prewomb to tomb. **Cell**. Marzo

Tendencias (2)



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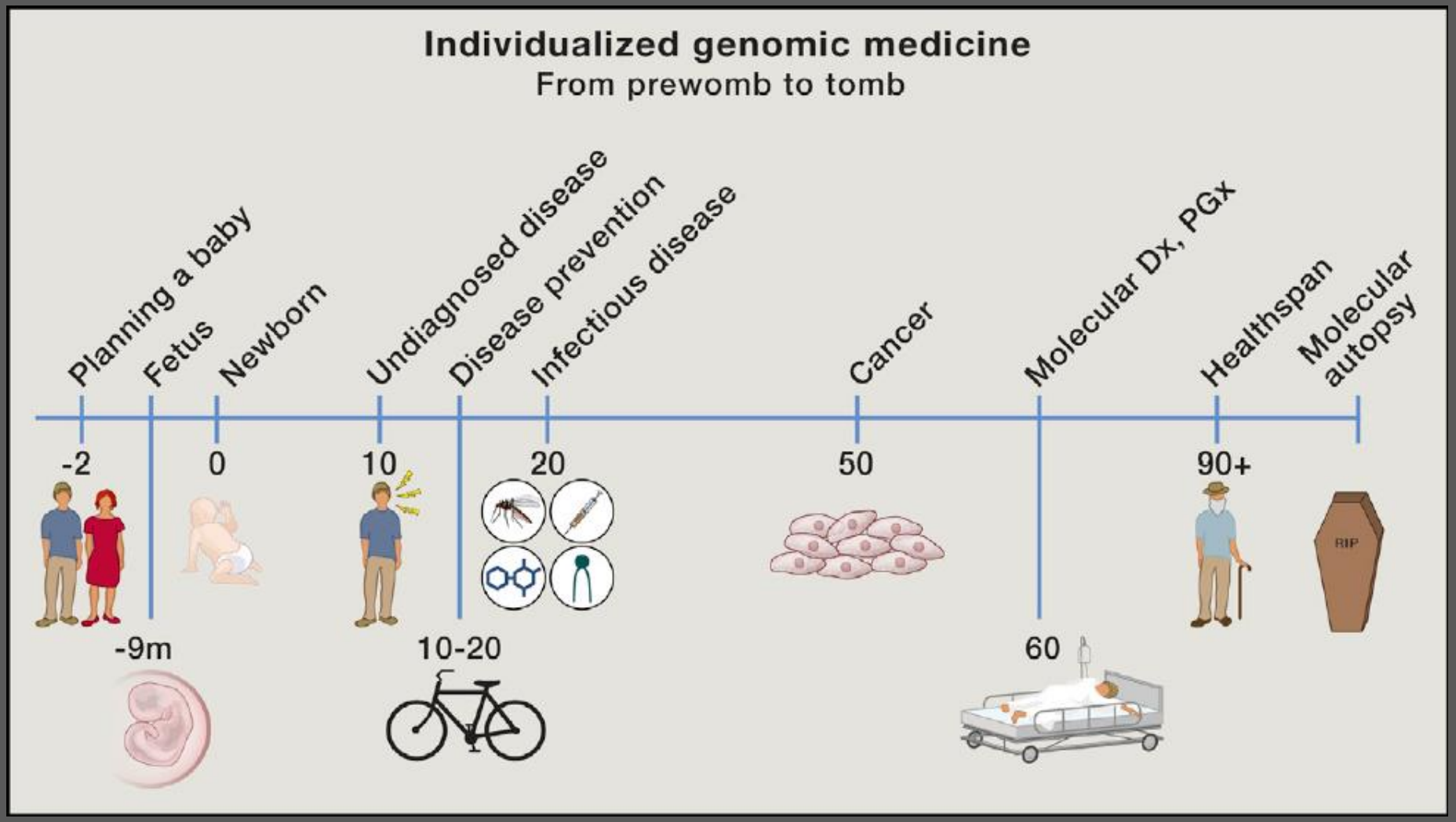
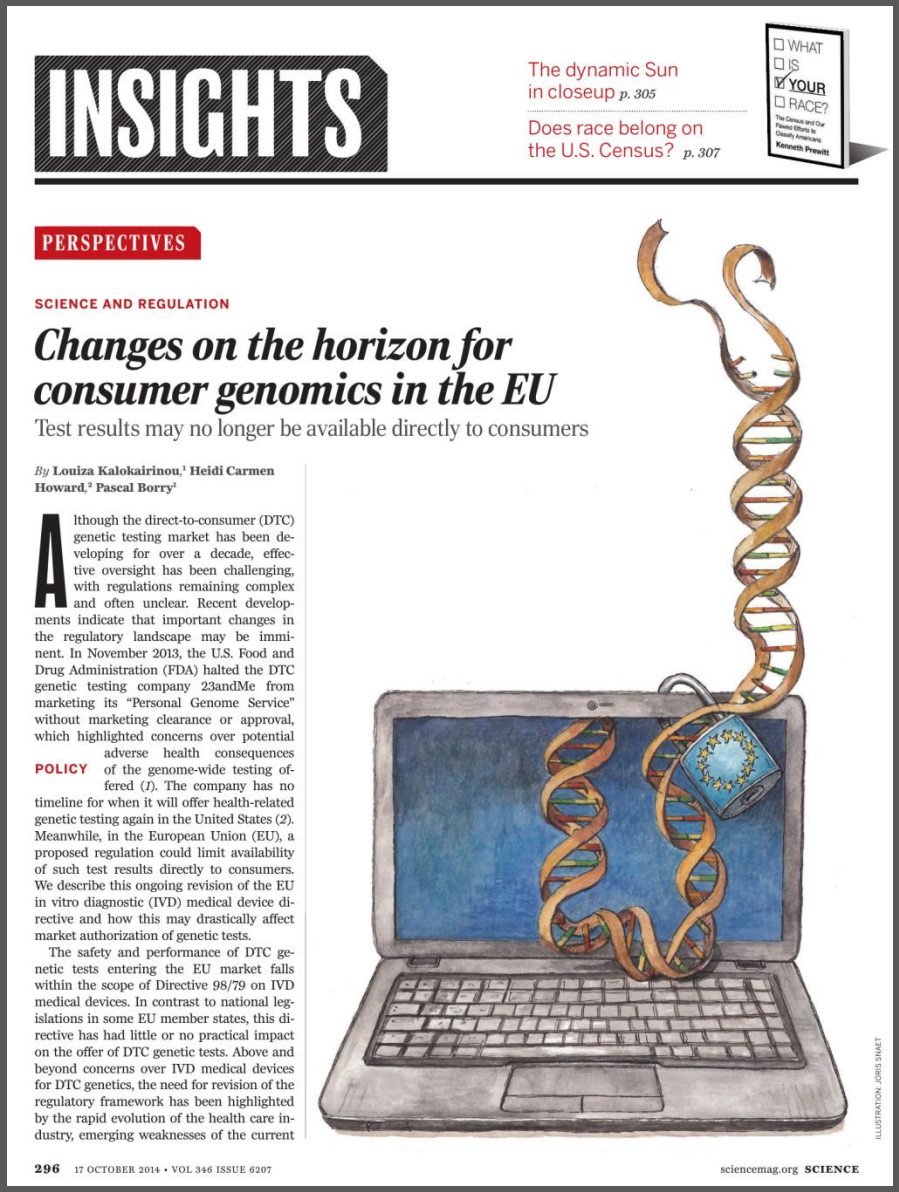


Topol (2014). Individualized Medicine from prewomb to tomb. **Cell**. Marzo

El incierto futuro de la Genómica Personal



INSIGHTS

The dynamic Sun in closeup *p. 305*

Does race belong on the U.S. Census? *p. 307*

PERSPECTIVES

SCIENCE AND REGULATION

Changes on the horizon for consumer genomics in the EU

Test results may no longer be available directly to consumers

By **Louiza Kalokairinou,[1] Heidi Carmen Howard,[2] Pascal Borry[1]**

POLICY

Although the direct-to-consumer (DTC) genetic testing market has been developing for over a decade, effective oversight has been challenging, with regulations remaining complex and often unclear. Recent developments indicate that important changes in the regulatory landscape may be imminent. In November 2013, the U.S. Food and Drug Administration (FDA) halted the DTC genetic testing company 23andMe from marketing its "Personal Genome Service" without marketing clearance or approval, which highlighted concerns over potential adverse health consequences of the genome-wide testing offered (*1*). The company has no timeline for when it will offer health-related genetic testing again in the United States (*2*). Meanwhile, in the European Union (EU), a proposed regulation could limit availability of such test results directly to consumers. We describe this ongoing revision of the EU in vitro diagnostic (IVD) medical device directive and how this may drastically affect market authorization of genetic tests.

The safety and performance of DTC genetic tests entering the EU market falls within the scope of Directive 98/79 on IVD medical devices. In contrast to national legislations in some EU member states, this directive has had little or no practical impact on the offer of DTC genetic tests. Above and beyond concerns over IVD medical devices for DTC genetics, the need for revision of the regulatory framework has been highlighted by the rapid evolution of the health care industry, emerging weaknesses of the current

ILLUSTRATION: JORIS SNAET

Kalokairinou et al (2014). **Science** . Octubre

Genética y Genómica del cáncer (1)

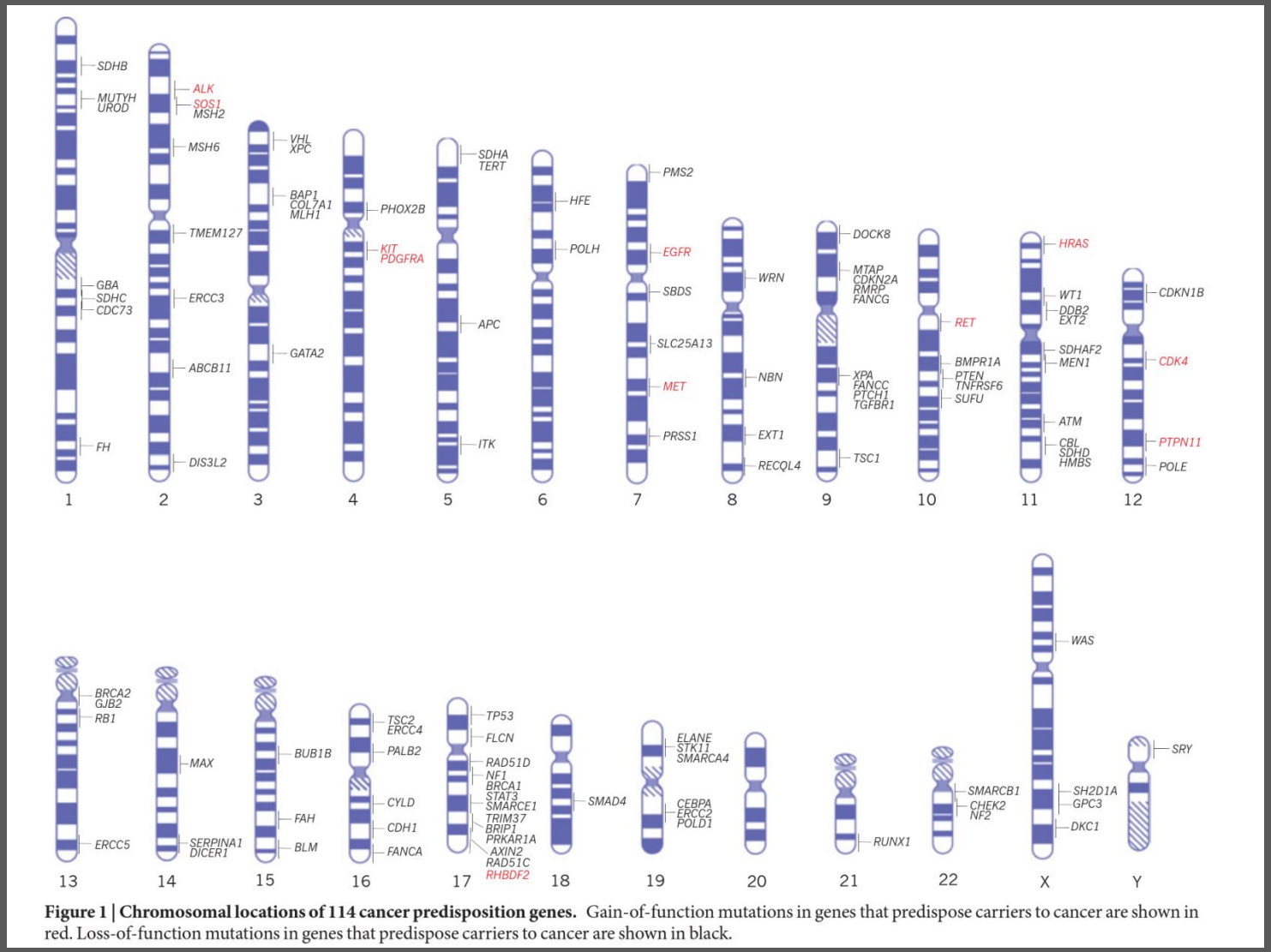


Figure 1 | Chromosomal locations of 114 cancer predisposition genes. Gain-of-function mutations in genes that predispose carriers to cancer are shown in red. Loss-of-function mutations in genes that predispose carriers to cancer are shown in black.

Rahman (2014). Realizing the promise of cancer predisposition genes. **Nature**. Enero 2014

Genética y Genómica del cáncer (2)

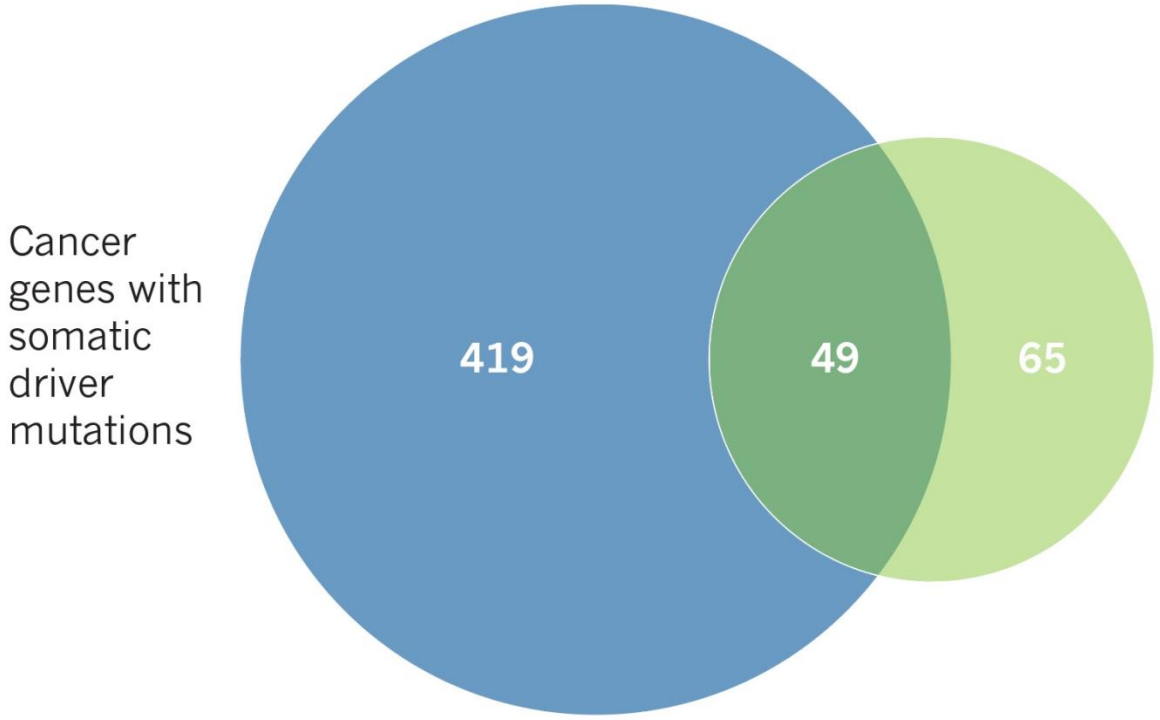


Figure 3 | Overlap between somatically mutated cancer genes and cancer predisposition genes (CPGs). 468 genes with somatic driver mutations in cancers are recorded in the COSMIC database of which 49 are also included within the 114 CPGs.

Rahman (2014). Realizing the promise of cancer predisposition genes. **Nature**. Enero 2014

Instituto de Medicina Genómica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Además del diagnóstico, los pacientes necesitan medicamentos

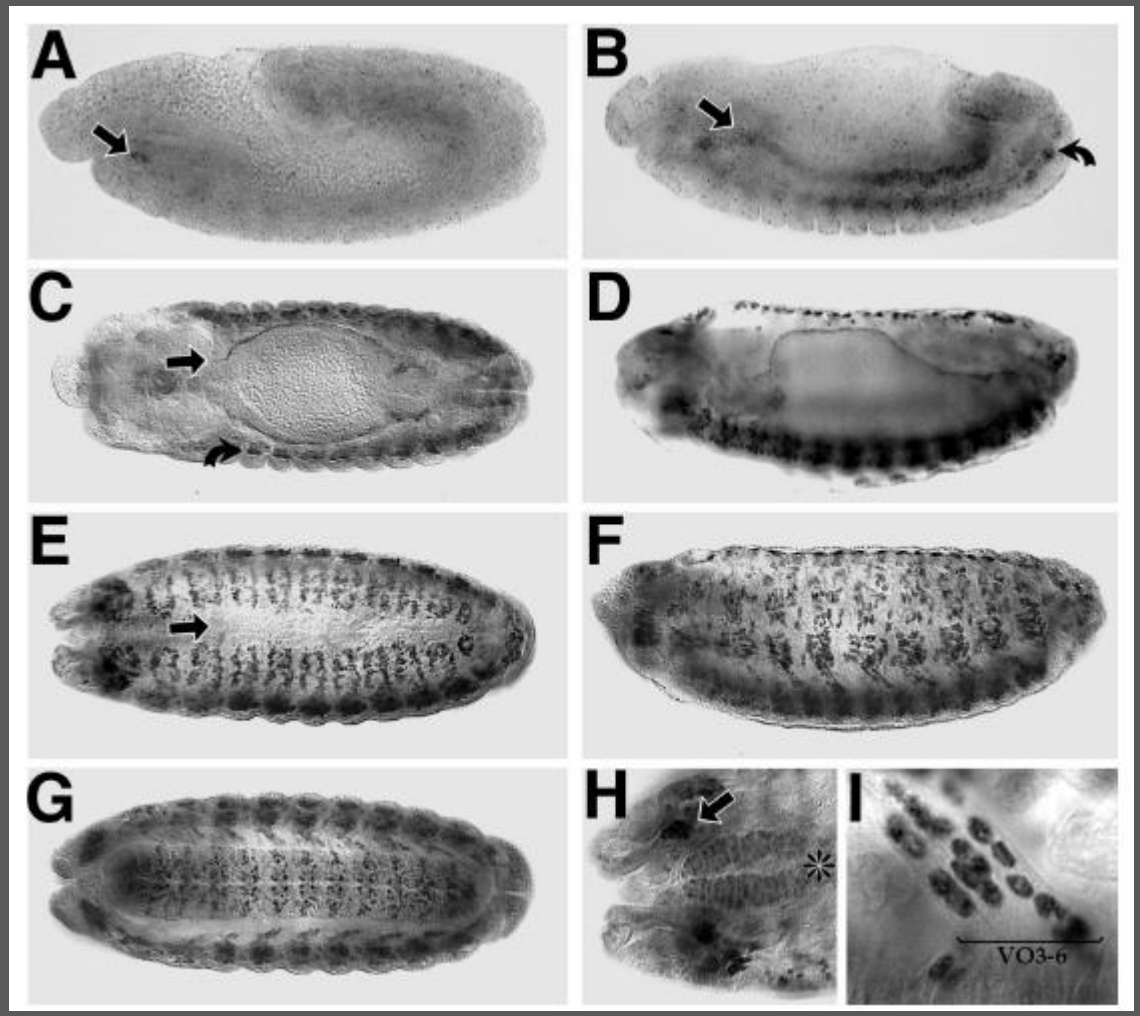
Investigación traslacional

Con los genomas de referencia se acelera nuestra comprensión de los procesos fisiológicos y las alteraciones patológicas: dianas terapéuticas y desarrollo de tratamientos

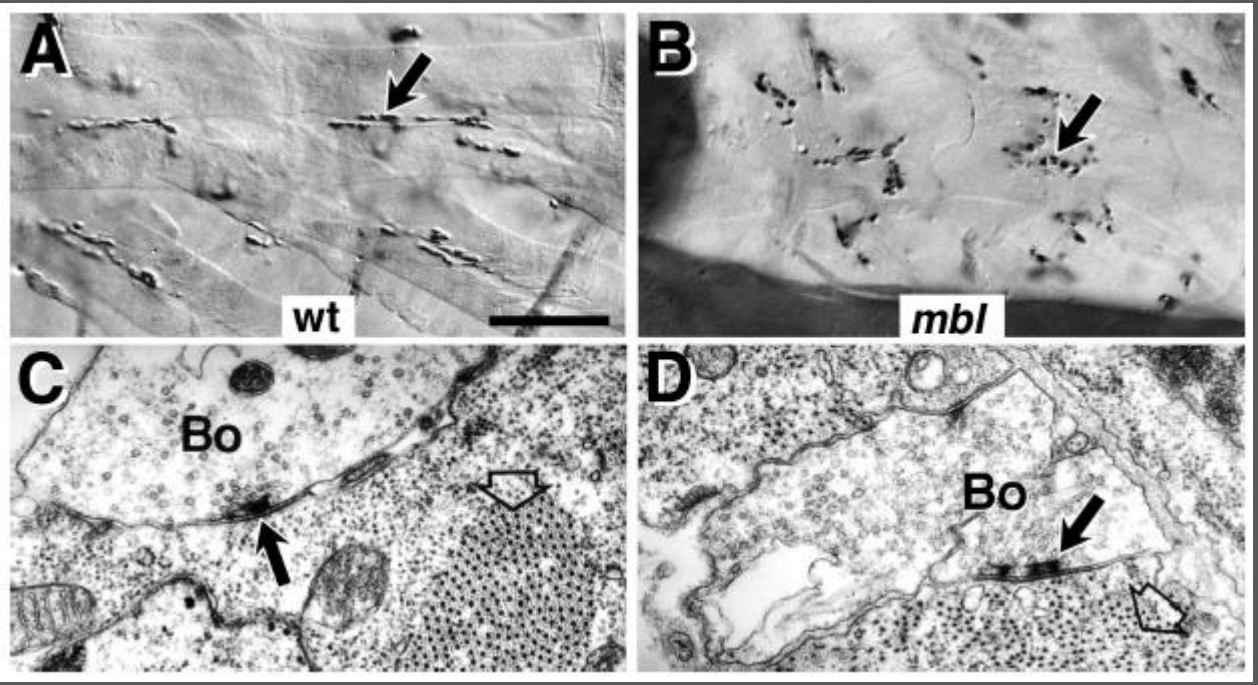
VALENTIA BioPharma, un laboratorio biofarmacéutico del Parque Científico de la Universitat de València

Creación de herramientas para la comprensión de las enfermedades genéticas humanas

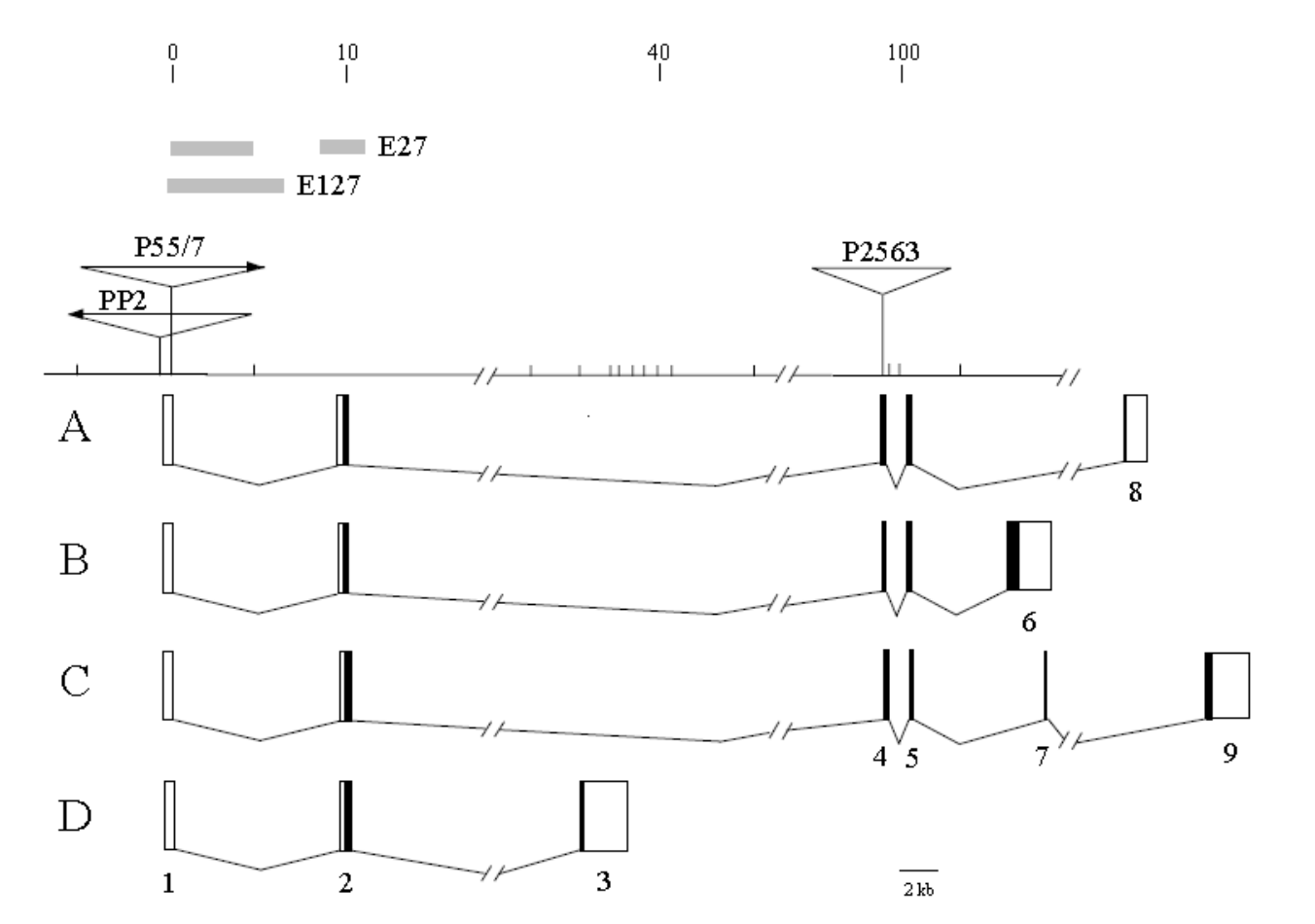
Analizando la expresión de los genes



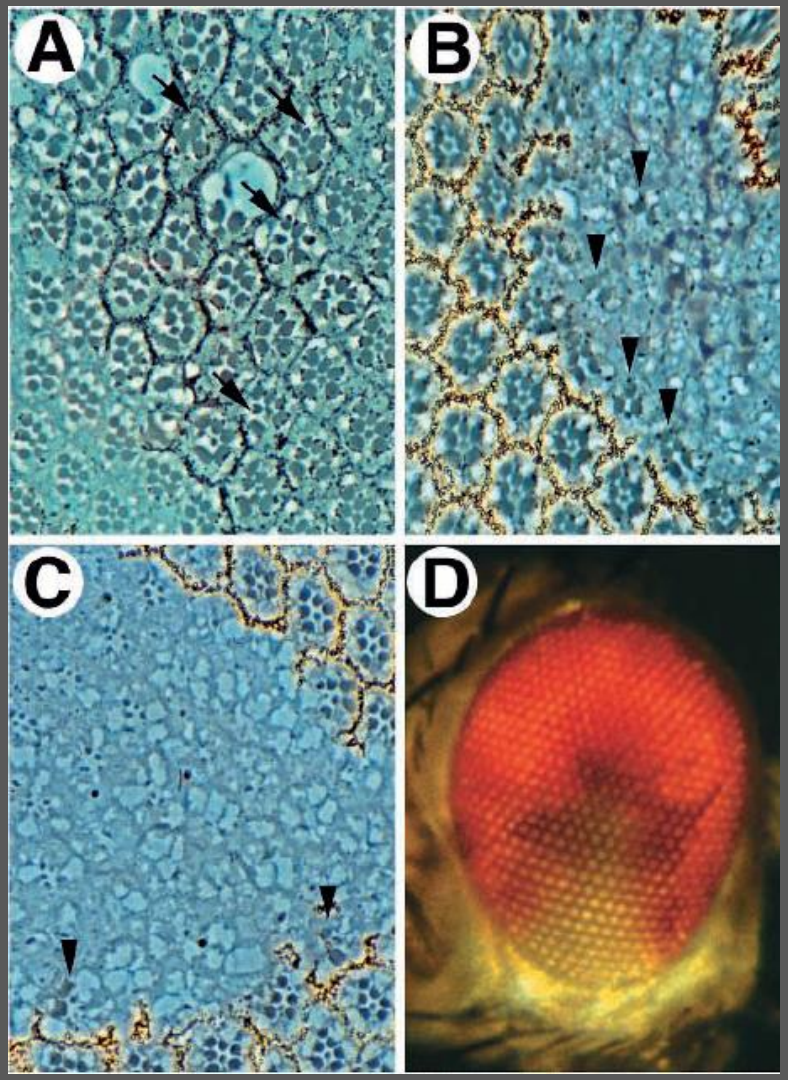
Analizando mutantes para comprender los fenómenos biológicos

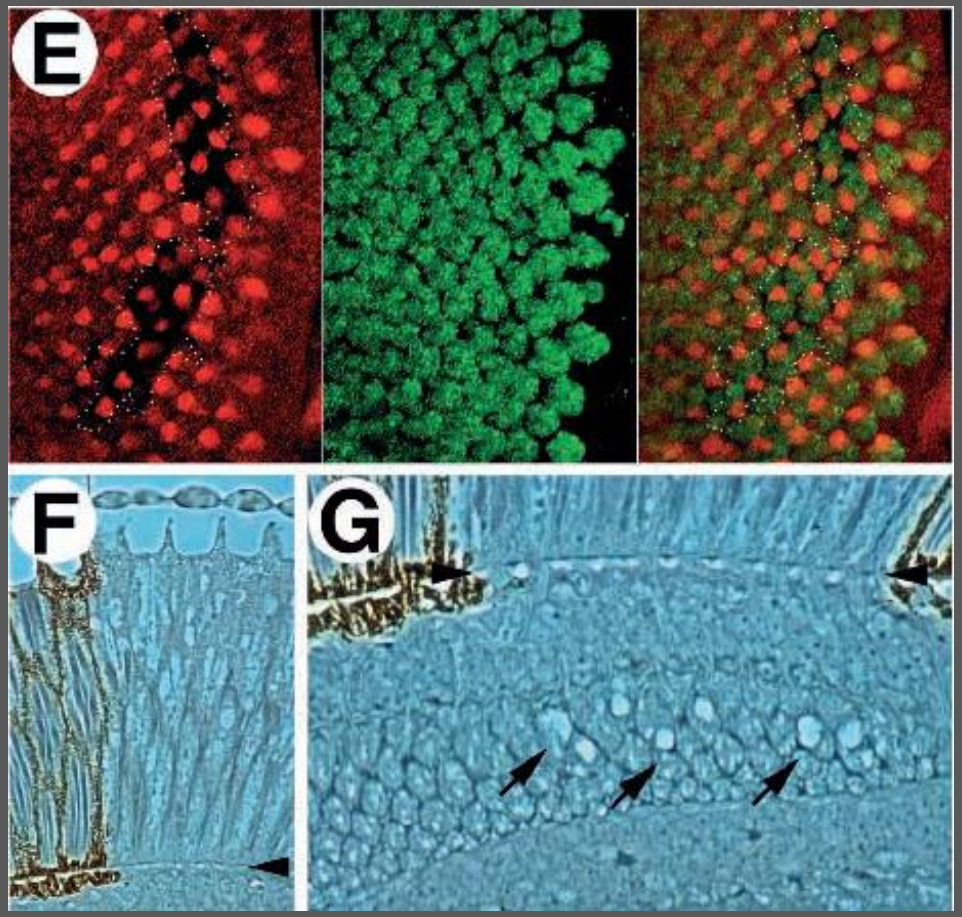


Aislando los genes relevantes

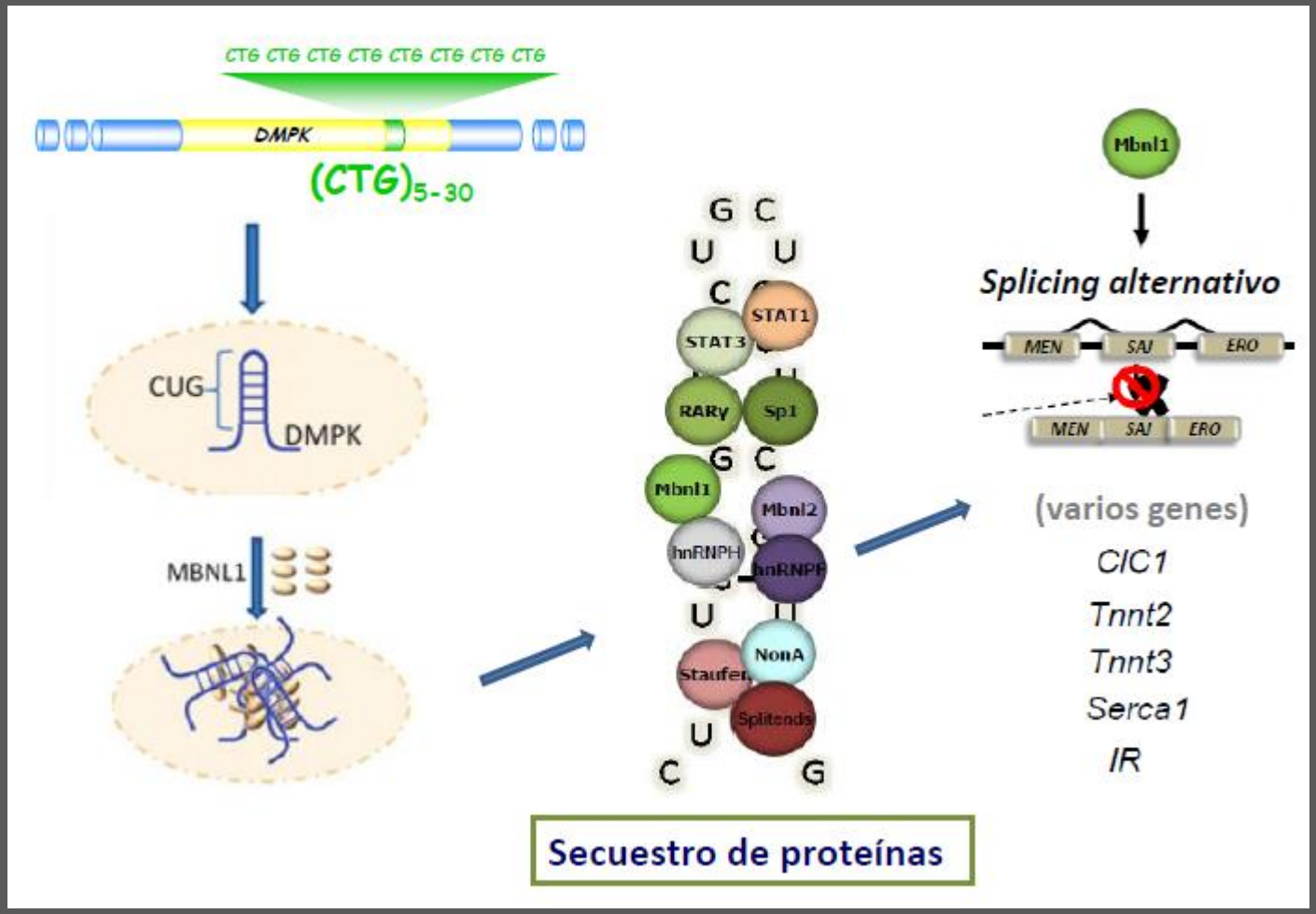


Manipulando el genoma de insectos para comprender las enfermedades humanas

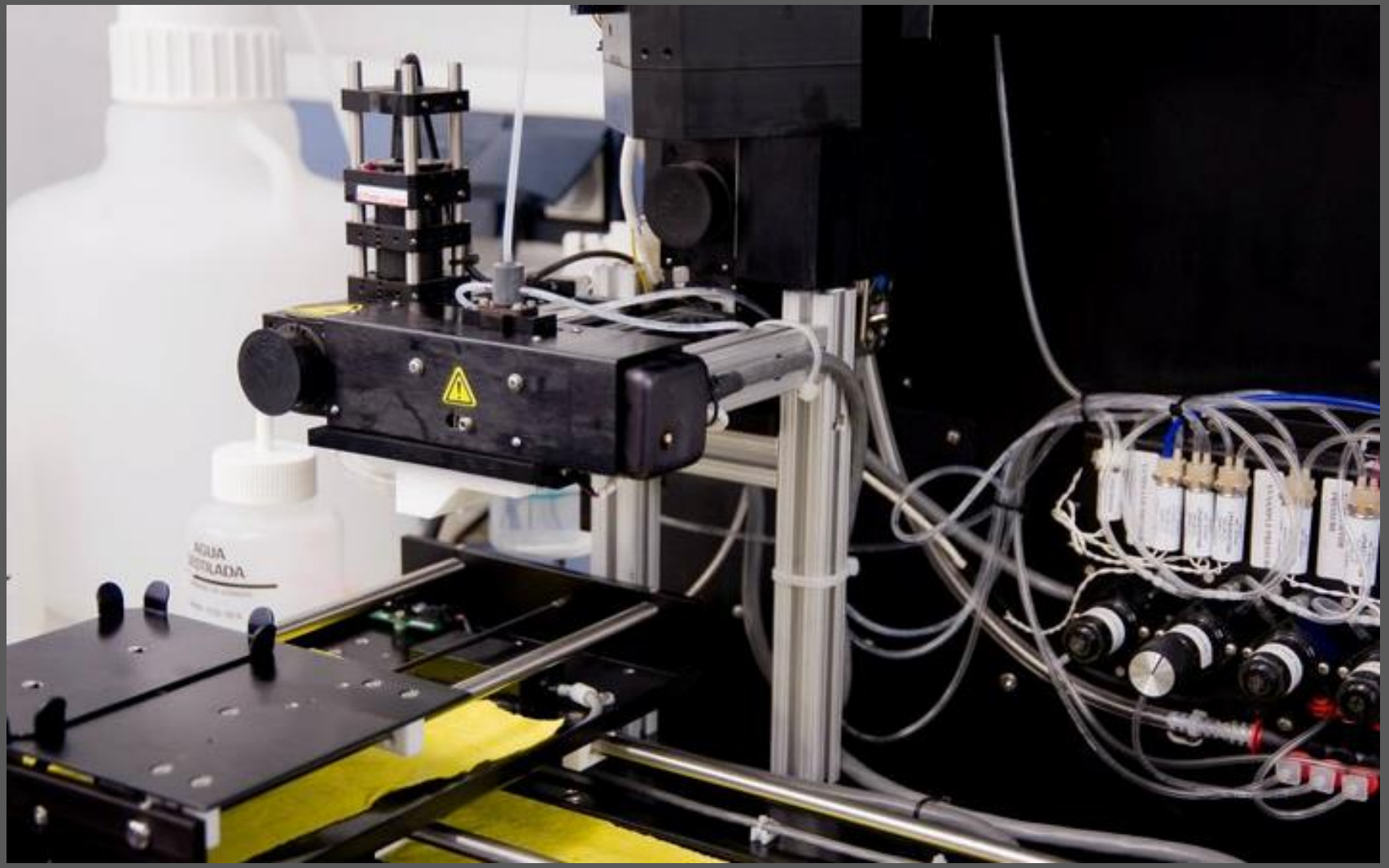




Mecanismo de patogénesis de la Distrofia miotónica



Industrializando los procesos



El resultado de Valentia BioPharma

Una batería de compuestos, potencialmente terapéuticos, para combatir la distrofia muscular miotónica, una enfermedad genética rara (todos ellos en desarrollo preclínico)

Orphan Drug Designation

A candidate molecule against Myotonic Dystrophy

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European Commission

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PHARMACEUTICALS - COMMUNITY REGISTER

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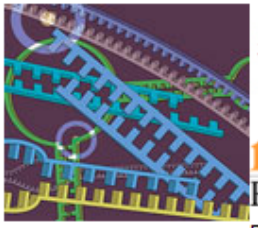
Register of designated Orphan Medicinal Products (alphabetical)

Product	EU Designation	Designated Orphan Indication	Sponsor	Designation date	Tradename EU Centralised Nr implemented by
(6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline-2,9-diol	EU/3/13/1226	Treatment of dystrophic myotonia	Valentia BioPharma S.L	16/01/2014	

Una nueva generación de fármacos basados en la intervención biológica a nivel del RNA



nature biotechnology

nature REVIEWS DRUG DISCOVERY

RNA-based therapeutics have generated significant attention in recent years due to their potential to treat a variety of chronic and rare diseases, and address targets that have proven to be intractable to antibody and small-molecule approaches. To highlight advances in delivery technologies and improved chemistry that have propelled the clinical advancement of RNA-based therapies (antisense, siRNAs, aptamers, microRNA mimics/anti-miRs and synthetic mRNA), *Nature Biotechnology* and *Nature Reviews Drug Discovery* present a joint focus on RNA-based therapies.

MicroRNA therapeutics: towards a new era for the management of cancer and other diseases

Rajesha Rupaimoole and Frank J. Slack

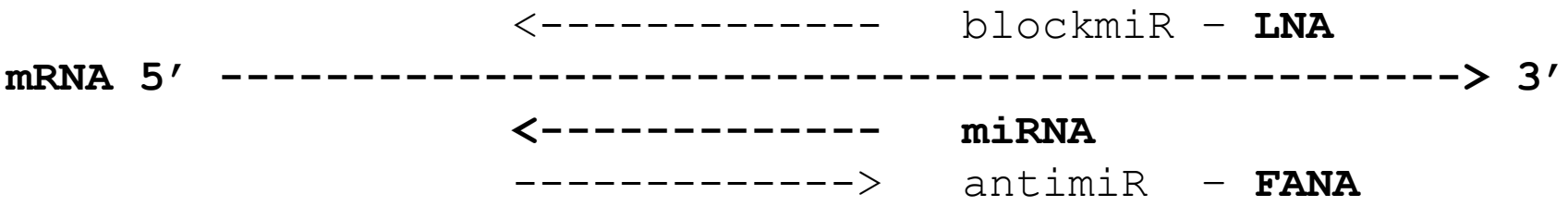
Abstract | In just over two decades since the discovery of the first microRNA (miRNA), the field of miRNA biology has expanded considerably. Insights into the roles of miRNAs in development and disease, particularly in cancer, have made miRNAs attractive tools and targets for novel therapeutic approaches. Functional studies have confirmed that miRNA dysregulation is causal in many cases of cancer, with miRNAs acting as tumour suppressors or oncogenes (oncomiRs), and miRNA mimics and molecules targeted at miRNAs (antimiRs) have shown promise in preclinical development. Several miRNA-targeted therapeutics have reached clinical development, including a mimic of the tumour suppressor miRNA miR-34, which reached phase I clinical trials for treating cancer, and antimiRs targeted at miR-122, which reached phase II trials for treating hepatitis. In this article, we describe recent advances in our understanding of miRNAs in cancer and in other diseases and provide an overview of current miRNA therapeutics in the clinic. We also discuss the challenge of identifying the most efficacious therapeutic candidates and provide a perspective on achieving safe and targeted delivery of miRNA therapeutics.

Ensayos clínicos en marcha

Table 1 | **Representative oligonucleotide-based drugs targeting miRNAs, repetitive RNAs and pre-mRNAs currently in clinical trials**

Company	Drug name	Chemistry	Mechanism of action	Target	Disease	Clinical status*	Refs
Mirna	MRX-34	dsRNA (liposomal nanoparticle formulation)	miRNA mimic	miR-34 targets	Solid tumours and haematological malignancies	Phase I	39,142
Regulus	RG-101	GalNAc-conjugated	miRNA inhibitor	miR-122	HCV	Phase II	143,144
	RG-012	NA	NA	miR-21	Alport syndrome	Phase I	145
	RG-125 (AZD4076)	GalNAc-conjugated	miRNA inhibitor	miR-103/107	Nonalcoholic steatohepatitis	Phase I	146
Roche	Miravirsen (SPC3649)	LNA	miRNA inhibitor	miR-122	HCV	Phase II	147–150
miRagen	MRG-201	NA	miRNA mimic	miR-29b targets	Cutaneous and pulmonary fibrosis	Phase I	–
	MRG-106	LNA	miRNA inhibitor	miR-155	Haematological malignancies	Phase I	–
BioMarin	Drisapersen (also known as GSK-2402968 or PRO051)	2′-O-methyl phosphorothioate	Exon skipping	Exon 51 of dystrophin pre-mRNA	DMD	Phase III (completed)	51,52,58
	BMN 044 (also known as PRO044)	2′-O-methyl phosphorothioate	Exon skipping	Exon 44 of dystrophin pre-mRNA	DMD	Phase II (discontinued)	151
	BMN 045 (also known as PRO045)	2′-O-methyl phosphorothioate	Exon skipping	Exon 45 of dystrophin pre-mRNA	DMD	Phase IIb (discontinued)	151
	BMN 053 (also known as PRO053)	2′-O-methyl phosphorothioate	Exon skipping	Exon 53 of dystrophin pre-mRNA	DMD	Phase I/II (discontinued)	151
Sarepta	Eteplirsen (also known as AVI-4658)	PMO	Exon skipping	Exon 51 of dystrophin pre-mRNA	DMD	Phase III	56
	SRP-4053	PMO	Exon skipping	Exon 53 of dystrophin pre-mRNA	DMD	Phase I/II	–
	SRP-4045	PMO	Exon skipping	Exon 45 of dystrophin pre-mRNA	DMD	Phase I	–
Ionis/Biogen	Nusinersen (also known as IONIS-SMN_{Rx})	2′-O-methoxyethyl and phosphorothioate chemistry	Exon inclusion	Intron 7 of *SMN2* pre-mRNA	SMA	Phase II, Phase III	57,152
	IONIS-DMPK-2.5_{Rx}	2′-O-methoxyethyl, cET and phosphorothioate chemistry	Gapmer	Exon 9 of *DMPK* mRNA	DM1	Phase I/IIa	–

Planteamiento de una terapia basada en el RNA



nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-04892-4 OPEN

miR-23b and *miR-218* silencing increase Muscleblind-like expression and alleviate myotonic dystrophy phenotypes in mammalian models

Estefania Cerro-Herreros[1,2,3], Maria Sabater-Arcis[1,2,3], Juan M. Fernandez-Costa[1,2,3], Nerea Moreno[1,2,3], Manuel Perez-Alonso[1,2,3], Beatriz Llamusi[1,2,3] & Ruben Artero[1,2,3]

Dónde seguir informados

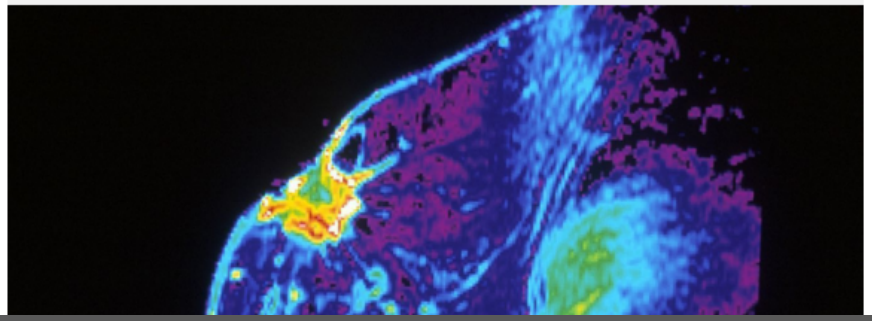
www.longevityworldforum.com/es/taller/

Disección del gen BRCA1 para mejorar el diagnóstico genético en cáncer de mama y ovario

POR GENÉTICA MÉDICA · PUBLICADO EL 14 DE SEPTIEMBRE DE 2018 ·

Amparo Tolosa, *Genética Médica News*

Investigadores de la Universidad de Washington han recreado y analizado el efecto de casi 4.000 mutaciones diferentes en el gen *BRCA1* con el objetivo de mejorar el consejo genético y la interpretación de las pruebas genéticas que estiman el riesgo a desarrollar cáncer de mama u ovario.

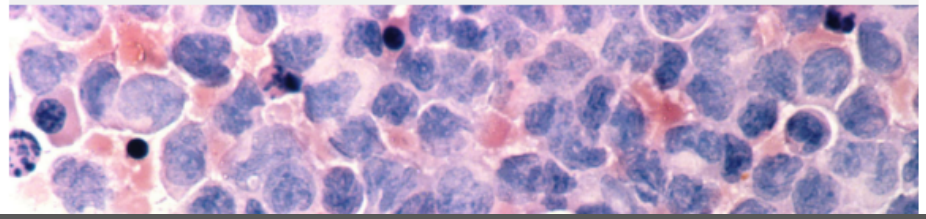


Desarrollada una nueva metodología molecular para la detección de niveles mínimos de células tumorales en leucemia

POR GENÉTICA MÉDICA · PUBLICADO EL 22 DE AGOSTO DE 2018 ·

Miguel Gallardo, *Unidad de Tumores Hematológicos, Programa Clínico, CNIO*

El equipo del Dr. Martínez-López, del departamento de Hematología Traslacional del Hospital Universitario 12 de Octubre, ha desarrollado una **nueva metodología basada en la técnica de *Next-Generation Sequencing* (NGS) por la cual es posible detectar niveles hasta ahora indetectables de enfermedad en pacientes con leucemia mieloide aguda** (LMA).



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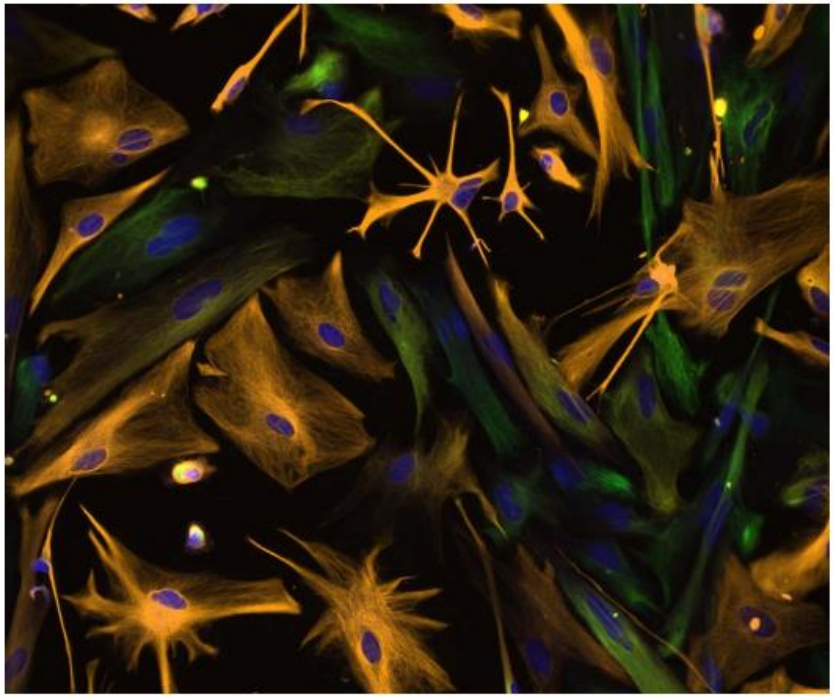
www.revistageneticamedica.com Volumen 5 Número 110 4 Septiembre 2018



En este número de Genetica Médica News:

- Desarrollada una nueva metodología molecular para la detección de niveles mínimos de células tumorales en leucemia.
- El descubrimiento de un nuevo tipo de célula pulmonar proporciona nuevas formas de estudiar la fibrosis quística.
- Corrigen una mutación responsable del síndrome de Marfan en embriones humanos.
- La FDA aprueba una terapia basada en ARN de interferencia para tratar una enfermedad rara.

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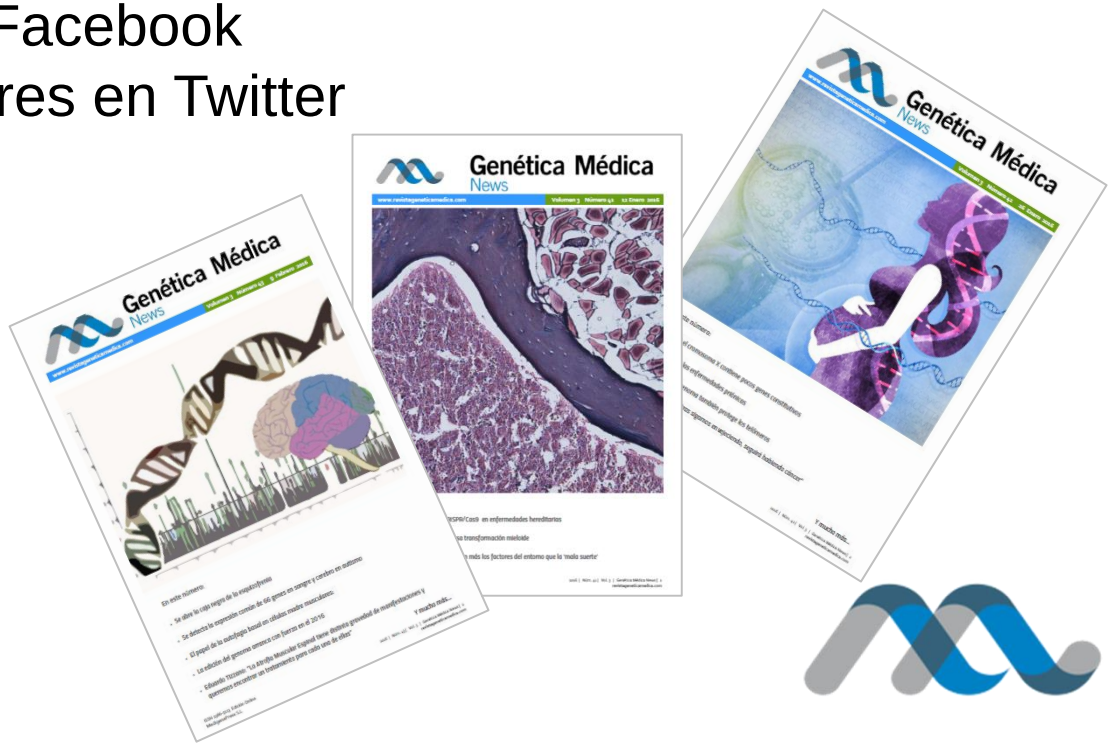

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11 lecturas recomendadas sobre Epigenética y Enfermedades

POR GENÉTICA MÉDICA · 10 DE NOVIEMBRE DE 2017

***Amparo Tolosa**, Genética Médica News*

El término epigenética hace referencia al conjunto de elementos que regulan la expresión de los genes sin modificar la secuencia del ADN y hacen posible que los diferentes tipos de células y tejidos expresen unos genes y no otros, y además, lo hagan en el momento adecuado.

El término epigenética hace referencia al conjunto de elementos que regulan la expresión de los genes sin modificar la secuencia del ADN. Imagen: Darryl Leja, National Human Genome Research institute (www.genome.gov)

Desde la aparición del término "epigenética" numerosos estudios han profundizado en el tema y en la actualidad existe una extensa bibliografía sobre los diferentes mecanismos epigenéticos, su participación durante el desarrollo, relación con diferentes enfermedades humanas y aproximaciones para modificarlos.

¡ Gracias por vuestra atención!

Manuel Pérez-Alonso
Departamento de Genética
Universitat de València

http://es.linkedin.com/in/manuelperezalonso