eНано

Генетические технологии для профилактической и персонализированной медицины

Артем Елмуратов

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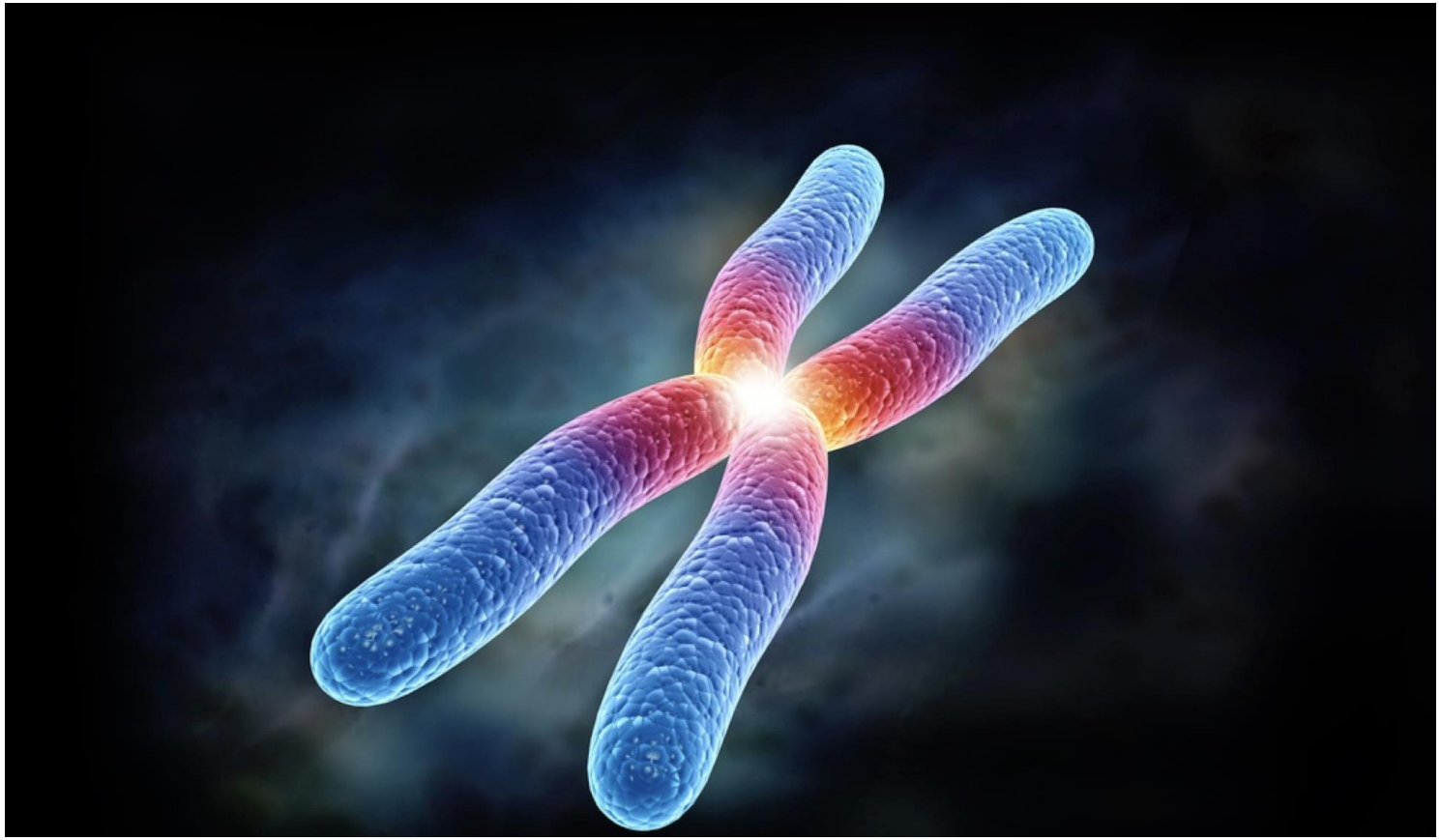
Со-основатель и директор по развитию медико-генетического центра Genotek

Научный сотрудник отдела биоинформатики Института Биомедицинской Химии им. В.Н. Ореховича РАН

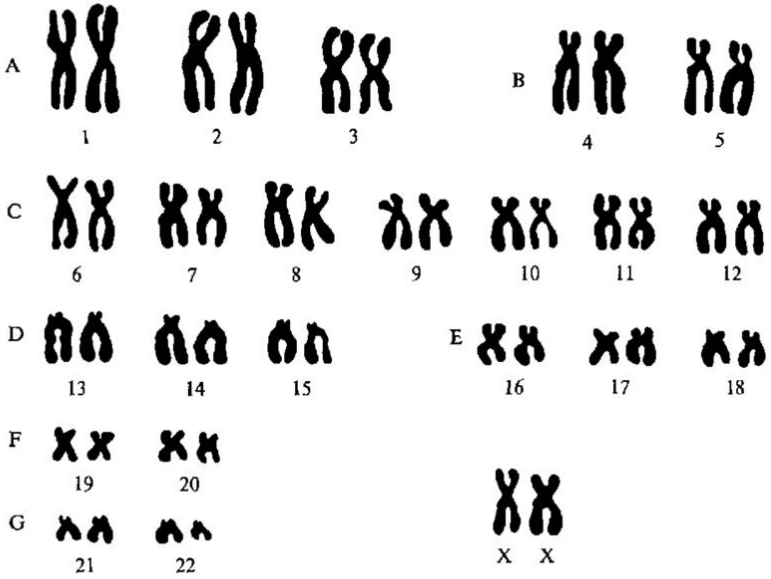
ДНК передает наследственную информацию



Содержится в каждой клетке и практически одинакова во всех клетках организма

50% от матери
50% от отца

23 хромосомы

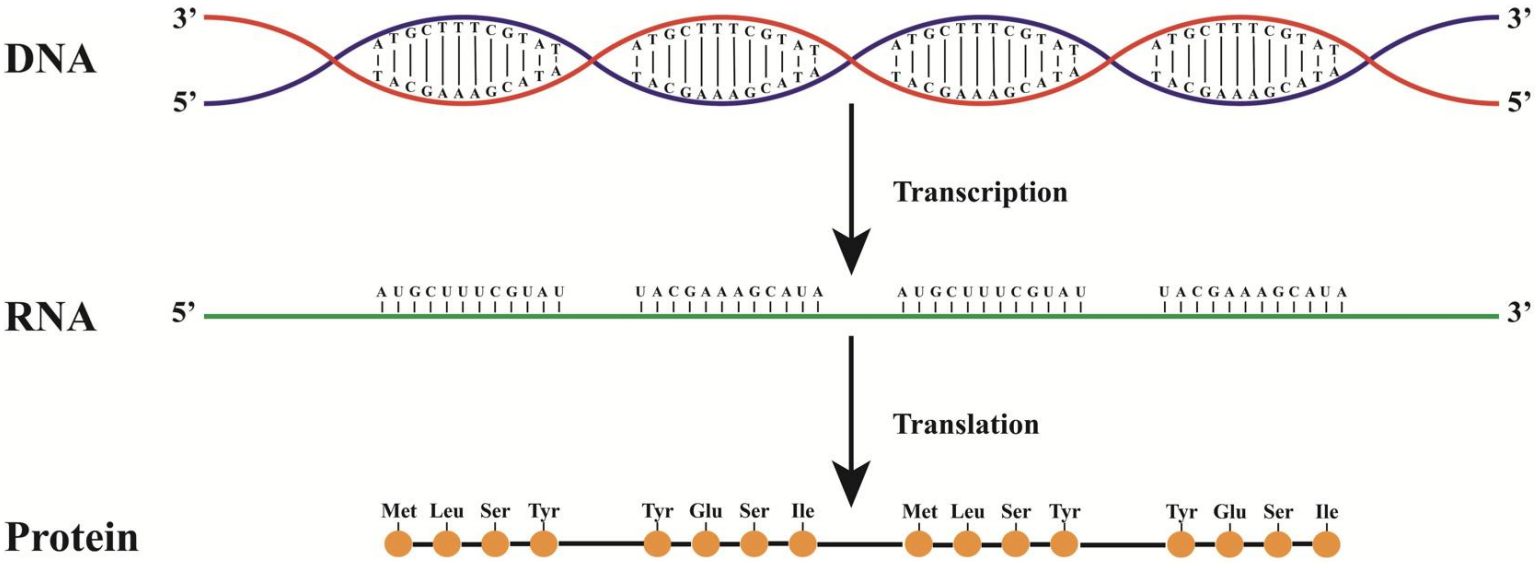


22 – аутосомы
23-я пара – половые

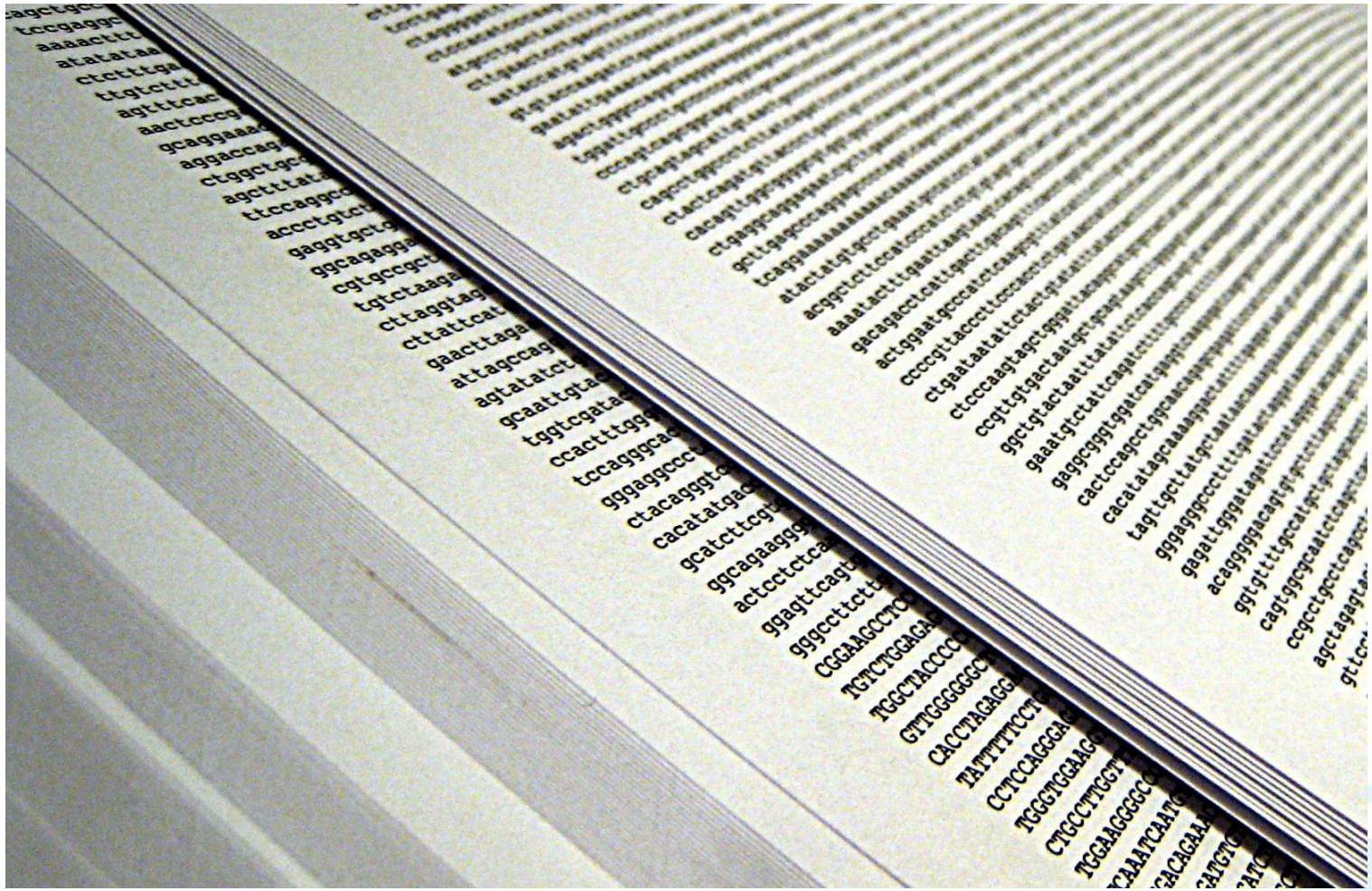
XX – женщина
XY - мужчина

Центральная догма молекулярной биологии

Центральная догма молекулярной биологии



Геном человека > 3 миллиардов пар «букв»

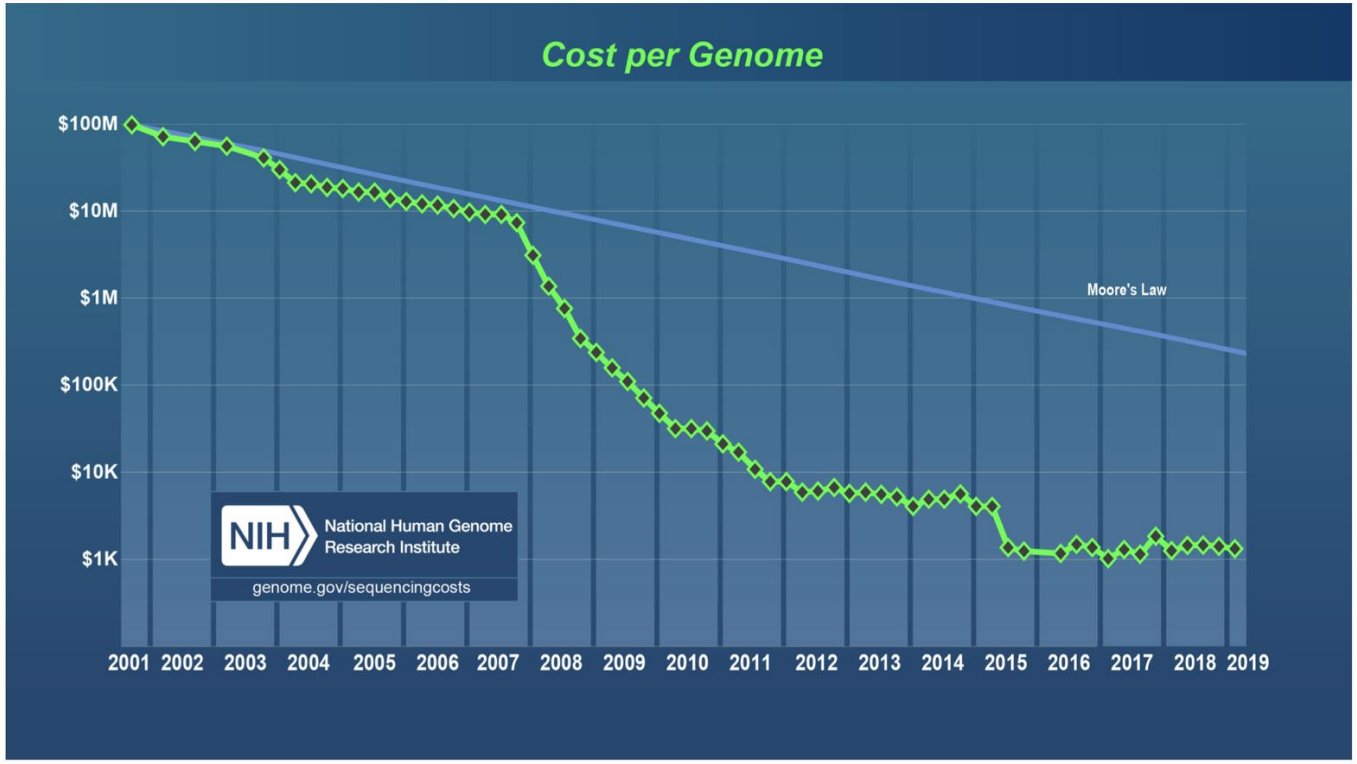


2001-й год. Первый геном человека

В 2001-м году были опубликованы предварительные результаты проектов «Геном человека»

Стоимость государственного проекта составила 3 миллиарда долларов США

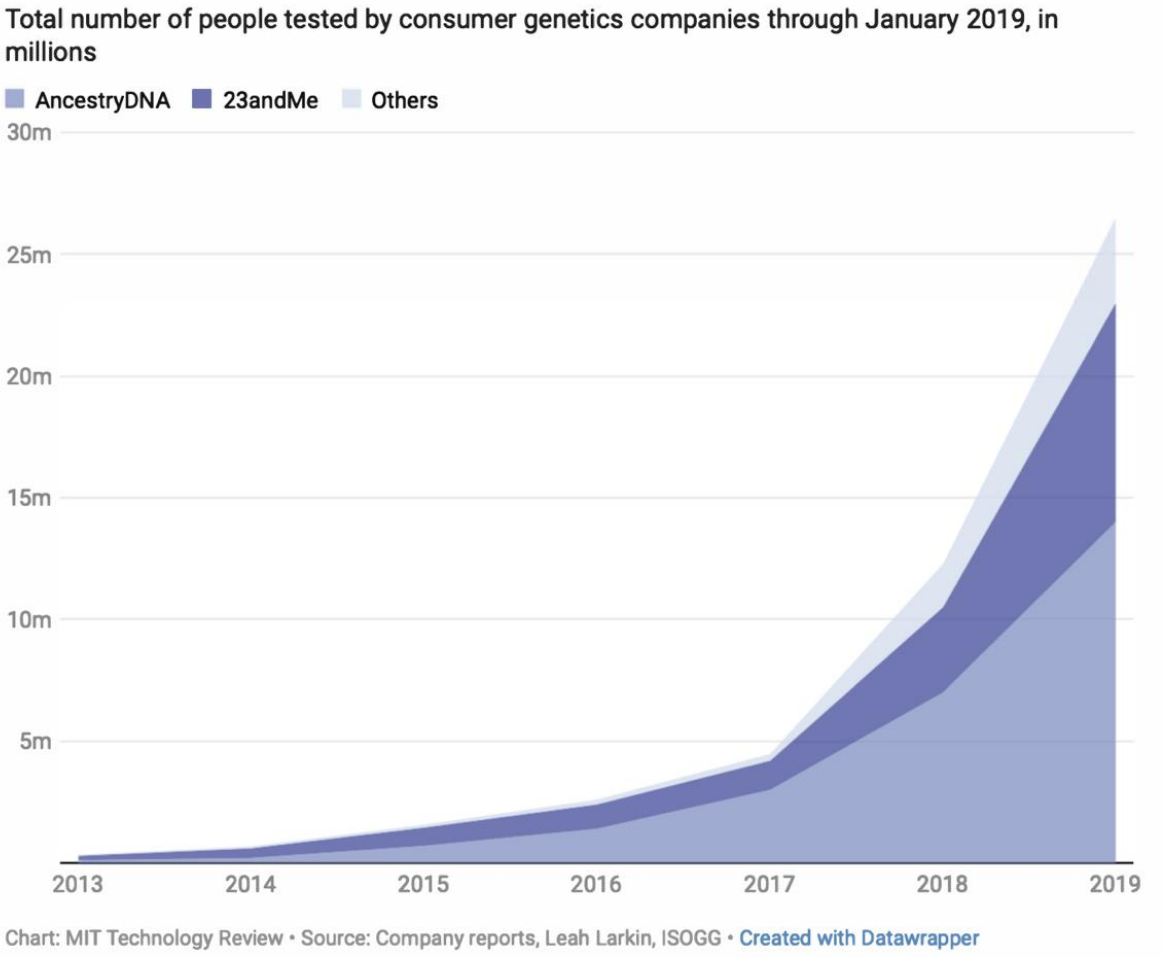
«Генетическая революция»



Технологии секвенирования («прочтения») ДНК развиваются быстрее закона Мура

За 15 лет цена прочтения генома снизилась практически в 100 000 раз

Развитие DTCG рынка



DTCG – direct-to-consumer genetics, генетические тесты, которые человек может пройти без назначения врача

Подобные тесты прошли более 10% американцев. Сейчас активно растут рынки других стран

Genotek

Основана в 2010 году выпускниками МГУ им. М.В. Ломоносова

Собственная высокопроизводительная лаборатория

Инвесторы: “ФармСтандарт “, Genome Ventures и др.

Медицинская лицензия, ISO менеджмент качества и независимый аудит качества

Genotek

Направления деятельности компании:

1

DTCG генетические тесты

2

Диагностика наследственных заболеваний

3

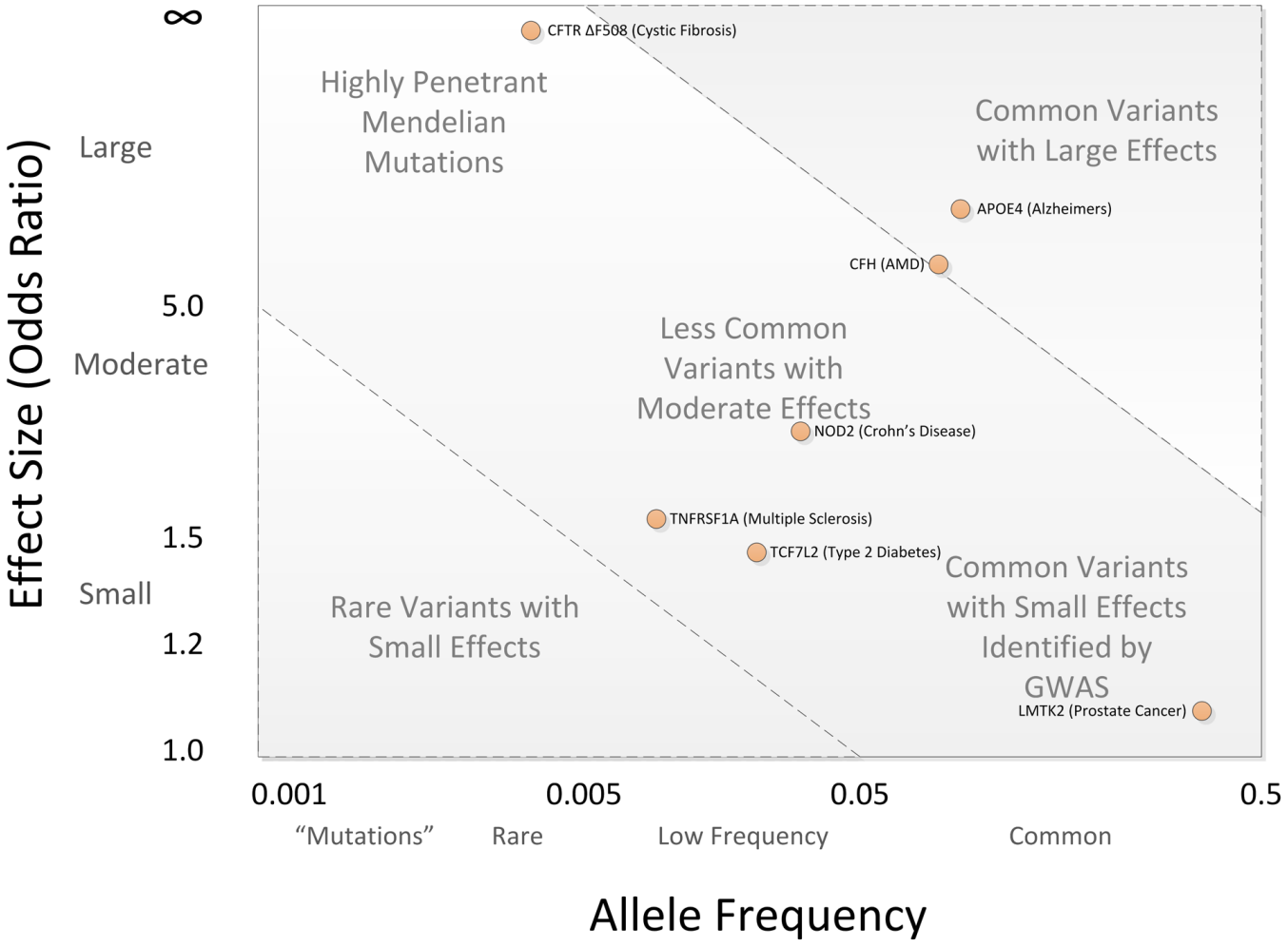
Услуги для НИИ и фармацевтических компаний

4П-медицина

1. Персонализированная (personalized)
2. Превентивная (preventative)
3. Парситипативная (participatory)
4. Предиктивная (predictive)

Также это всё объединяют понятием «точная» медицина (precision medicine)

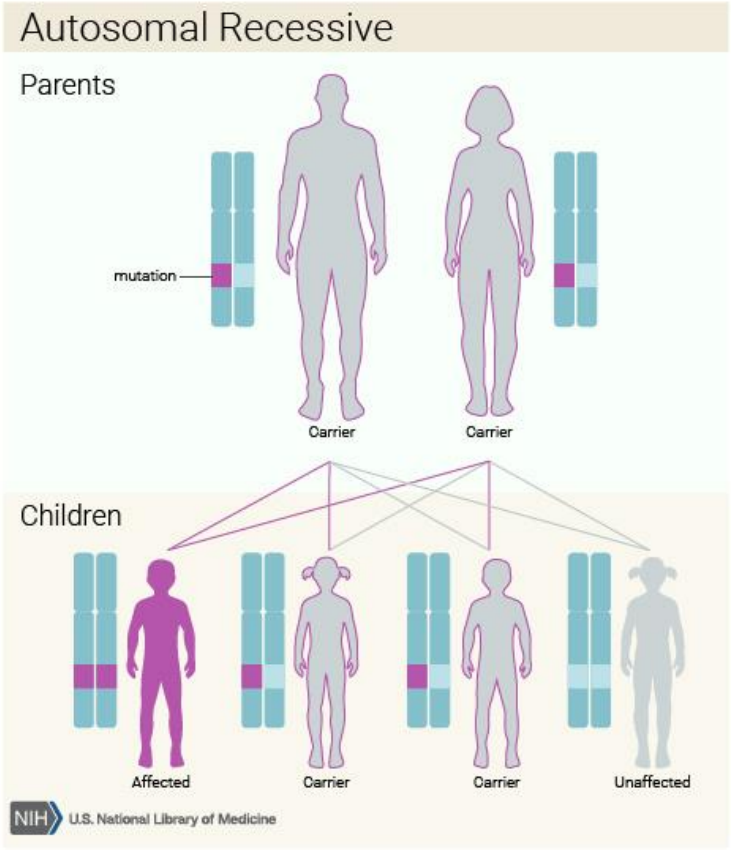
Вклад генетики в развитие заболеваний



Заболевания можно условно разделить на:

1. наследственные
2. мульти-факторные

Наследственные/моногенные заболевания

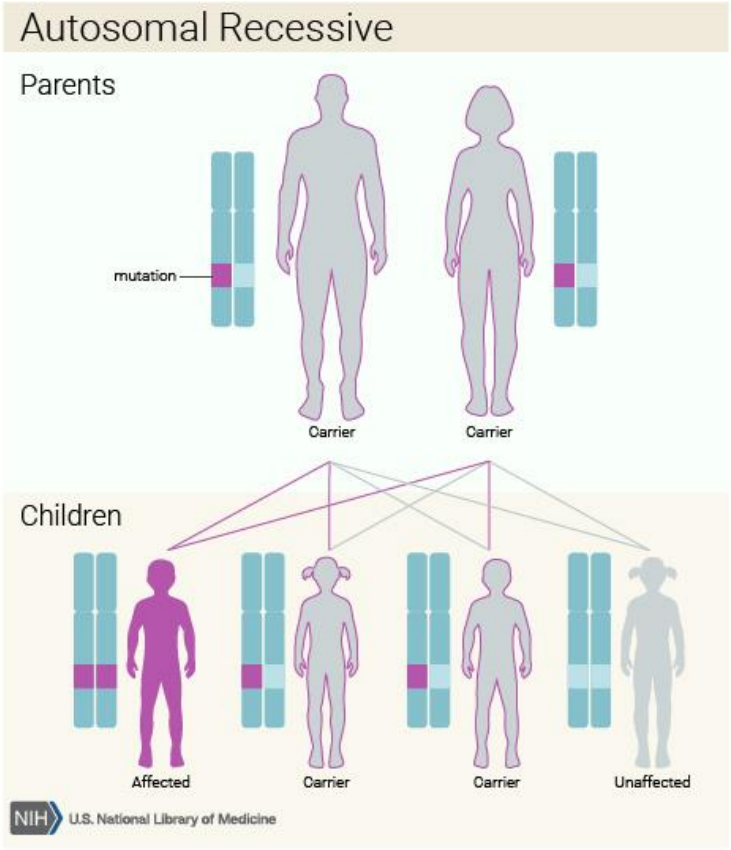


Более 6000 заболеваний, например:

- Талассемия
- Гемофилия
- Муковисцидоз
- Болезнь Тея-Сакса
- Злокачественная гипертермия и т.д.

С подобными патологиями рождаются суммарно несколько процентов детей

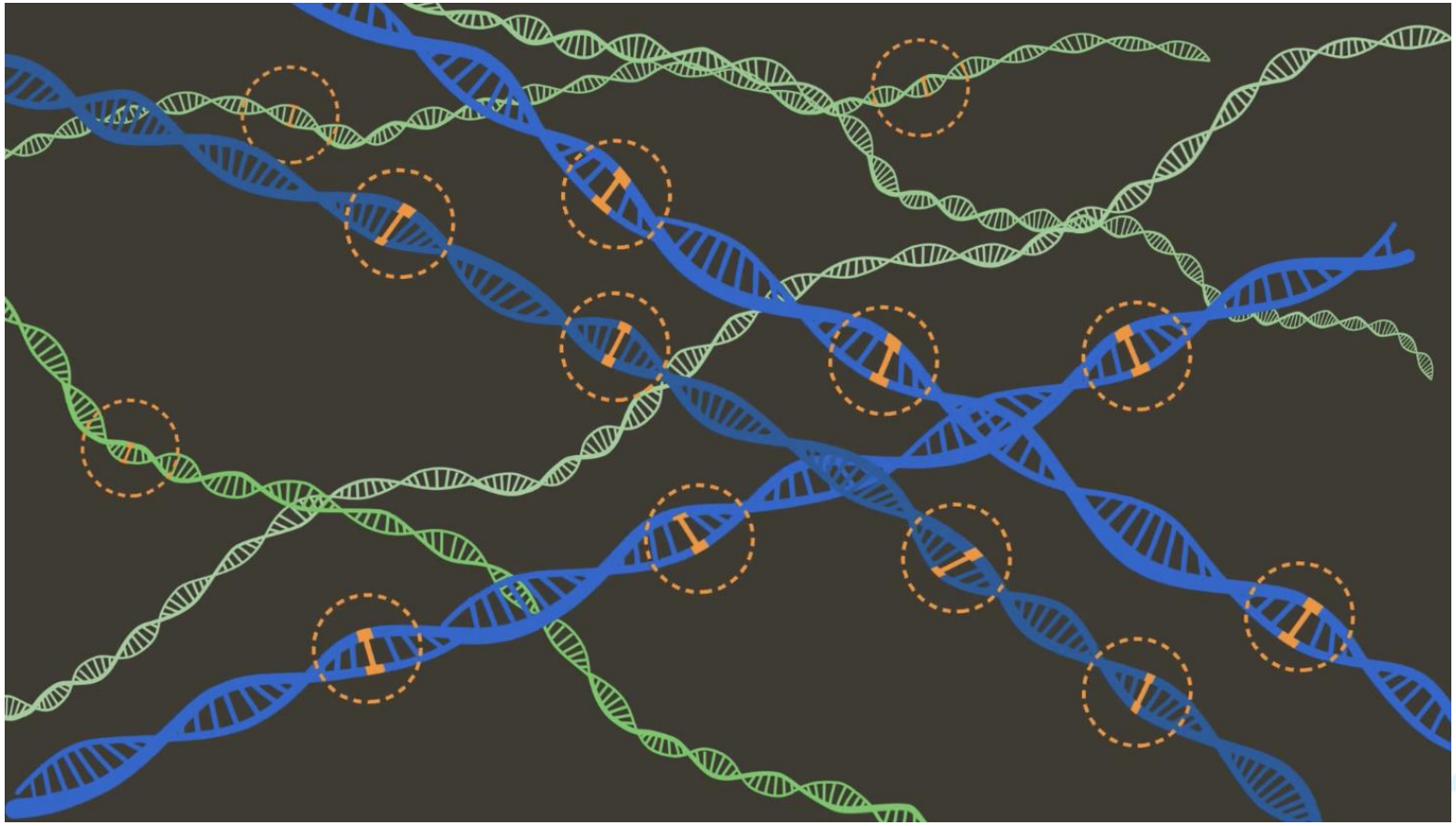
Планирование беременности



Каждый человек – носитель потенциально патогенных мутаций. Важно заранее определить, какие мутации есть у пары. Так как для ряда случаев есть эффективная профилактика, например ЭКО с ПГД

ЭКО – экстракорпоральное оплодотворение
ПГД – предимплантационная генетическая диагностика

Мультифакторные/полигенные заболевания

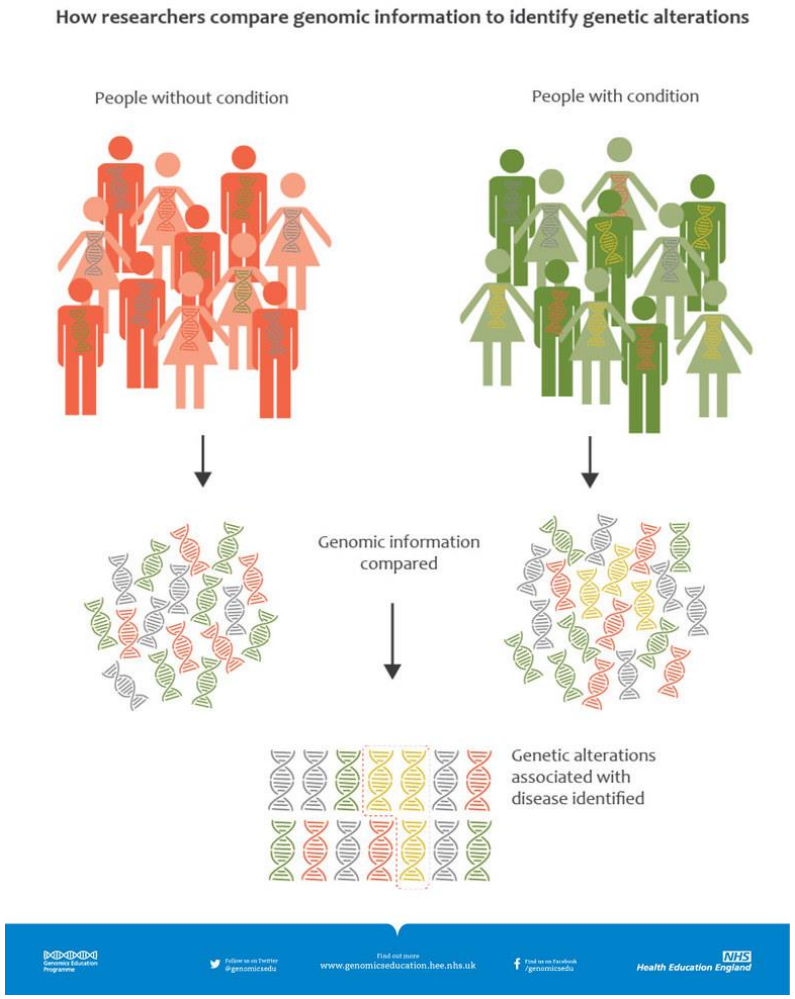


Риски развития заболеваний

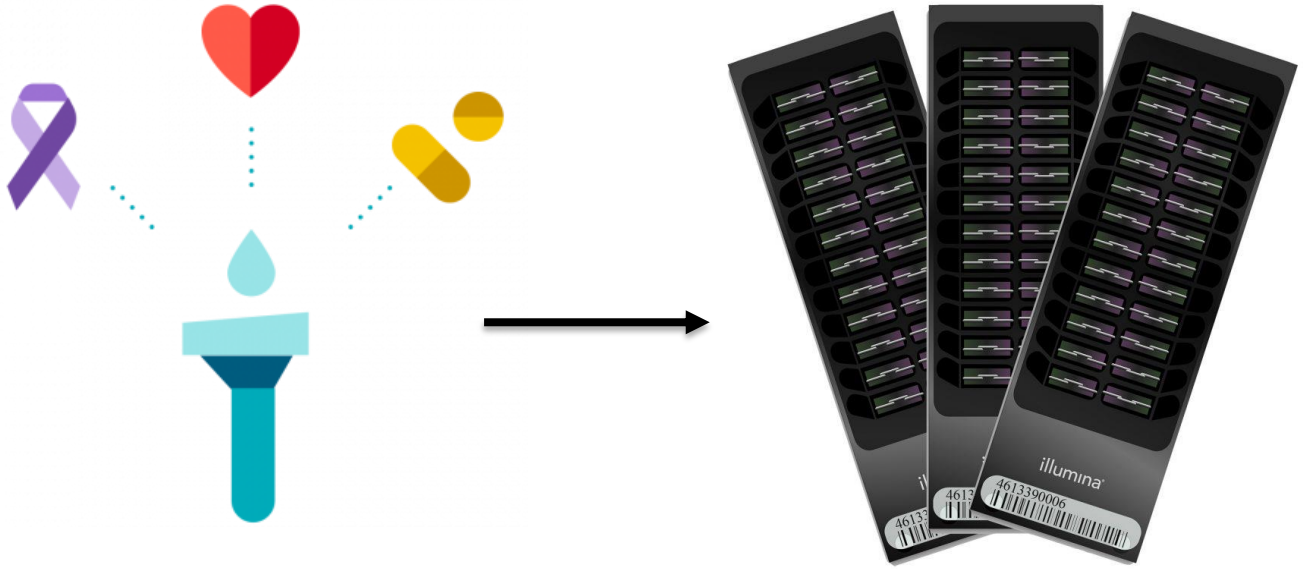
BRCA1, BRCA2 - Гены-супрессор опухолей (антионкогены). Мутации в этих генах увеличивают риск развития рака молочной железы у женщин с 12% до примерно 70%.

У Анджелины Джоли нашли мутацию в гене BRCA1

Мультифакторные/полигенные заболевания



Мультифакторные/полигенные заболевания

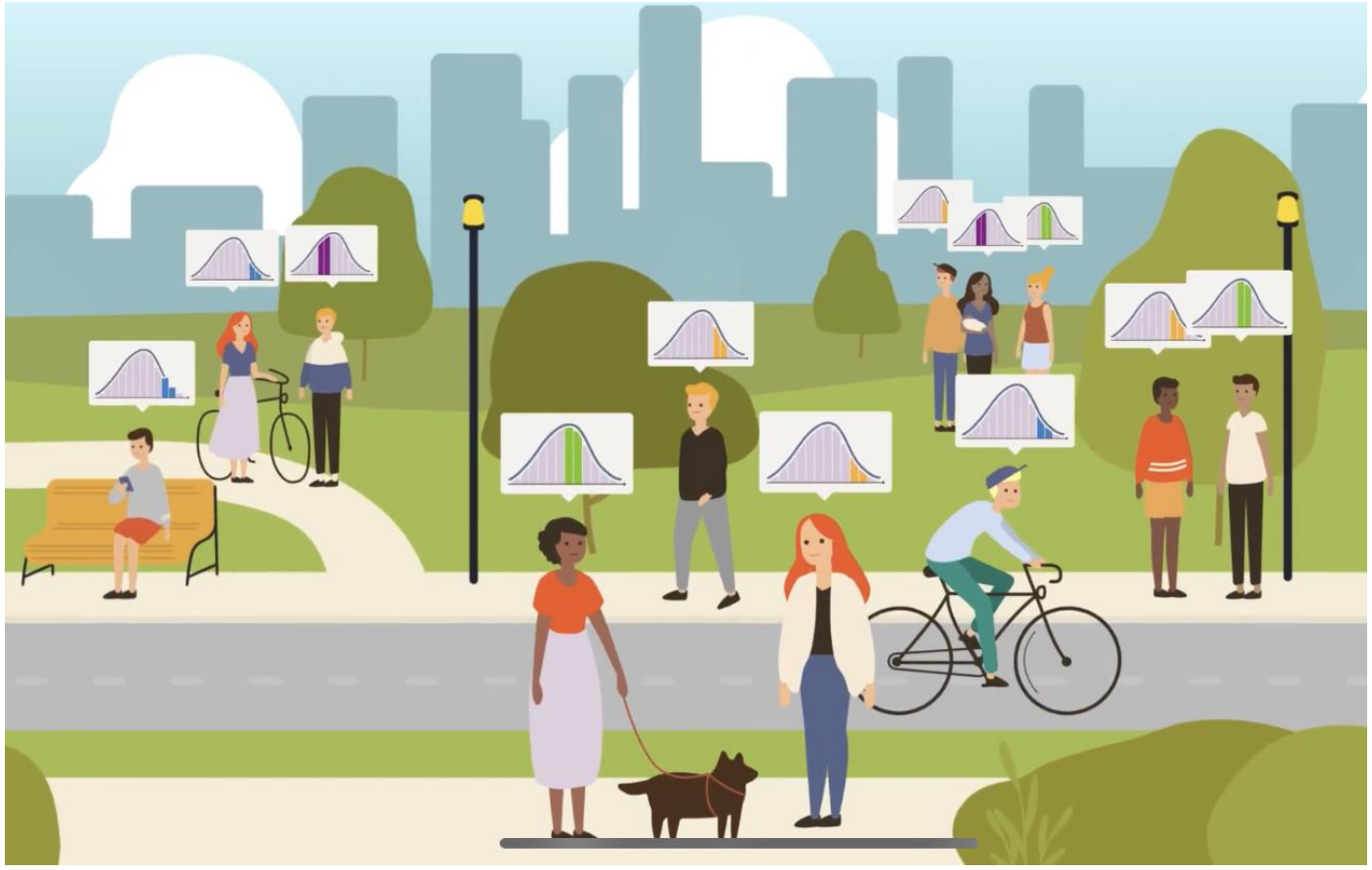


Для генетического тестирования обычно используется кровь или слюна, из которой выделяют ДНК. Далее считывается более 500 000 «точек» генома

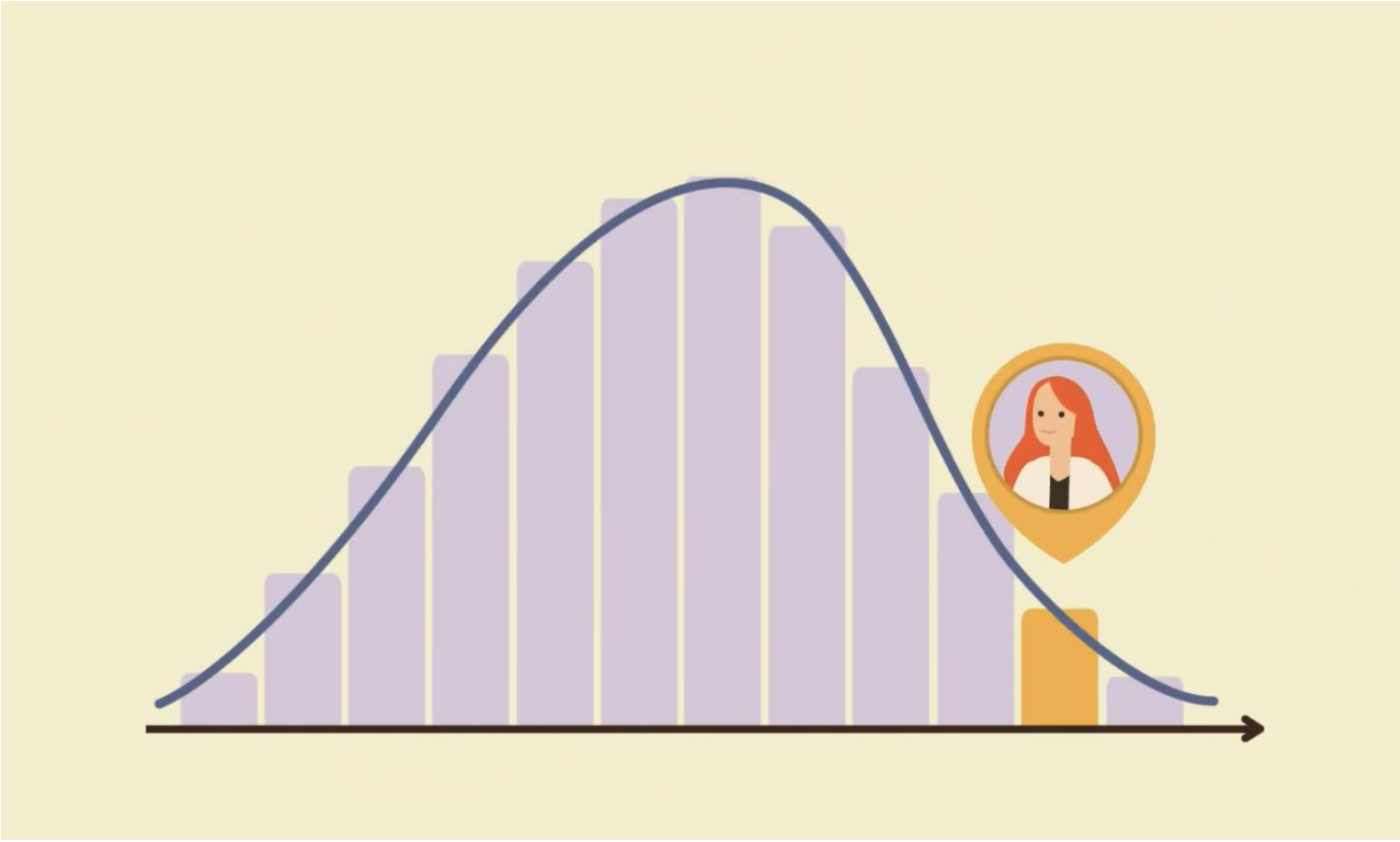
Ut enim ad minim veniam, quis nostrud

Мультифакторные/полигенные заболевания

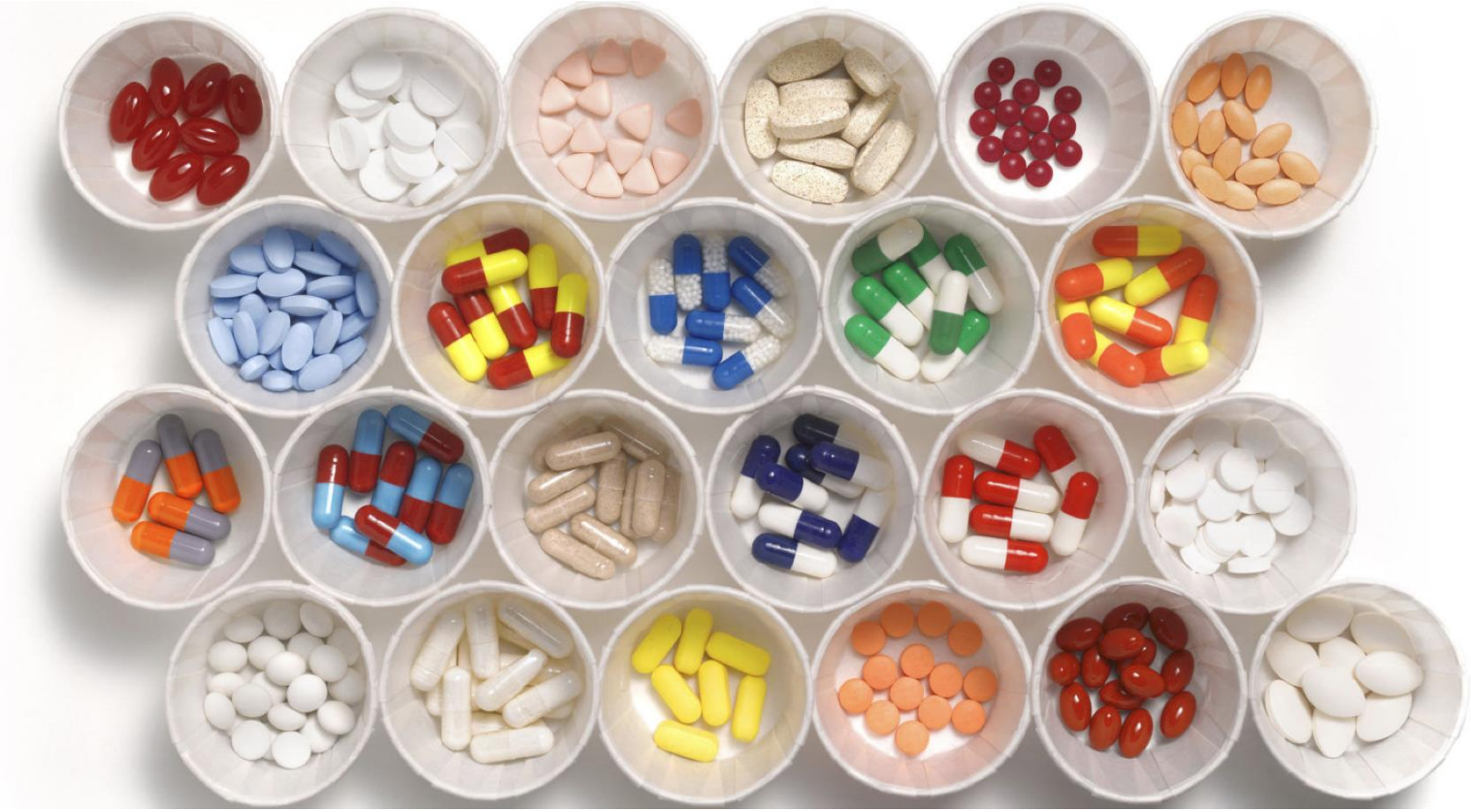
Мультифакторные/полигенные заболевания



Мультифакторные/полигенные заболевания



Фармакогенетика



Фармакогенетика

Уровень доказательности

Полиморфизм (SNP)

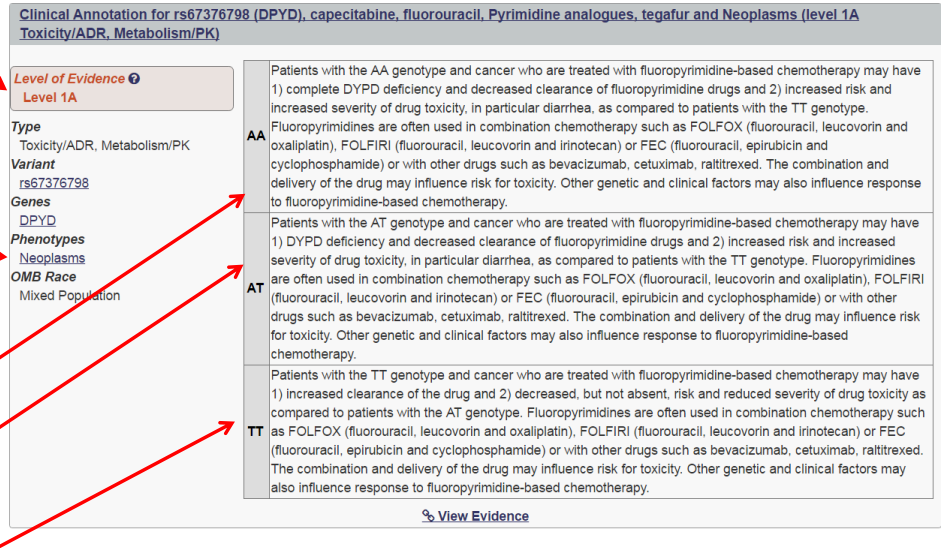
Ген

Заболевание

Токсично!

Токсично!

Безопасно



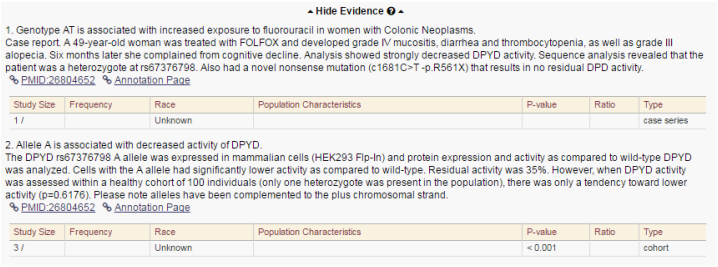
Clinical Annotation for rs67376798 (DPYD), capecitabine, fluorouracil, Pyrimidine analogues, tegafur and Neoplasms (level 1A Toxicity/ADR, Metabolism/PK)

Level of Evidence Level 1A

Type
Toxicity/ADR, Metabolism/PK
Variant
rs67376798
Genes
DPYD
Phenotypes
Neoplasms
OMB Race
Mixed Population

AA	Patients with the AA genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) complete DYPD deficiency and decreased clearance of fluoropyrimidine drugs and 2) increased risk and increased severity of drug toxicity, in particular diarrhea, as compared to patients with the TT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.
AT	Patients with the AT genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) DYPD deficiency and decreased clearance of fluoropyrimidine drugs and 2) increased risk and increased severity of drug toxicity, in particular diarrhea, as compared to patients with the TT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.
TT	Patients with the TT genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) increased clearance of the drug and 2) decreased, but not absent, risk and reduced severity of drug toxicity as compared to patients with the AT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.

View Evidence



Hide Evidence

1. Genotype AT is associated with increased exposure to fluorouracil in women with Colonic Neoplasms.
Case report. A 49-year-old woman was treated with FOLFOX and developed grade IV mucositis, diarrhea and thrombocytopenia, as well as grade III alopecia. Six months later she complained from cognitive decline. Analysis showed strongly decreased DPYD activity. Sequence analysis revealed that the patient was a heterozygote at rs67376798. Also had a novel nonsense mutation (c1681C>T -p.R561X) that results in no residual DPD activity.
PMID:26804652 Annotation Page

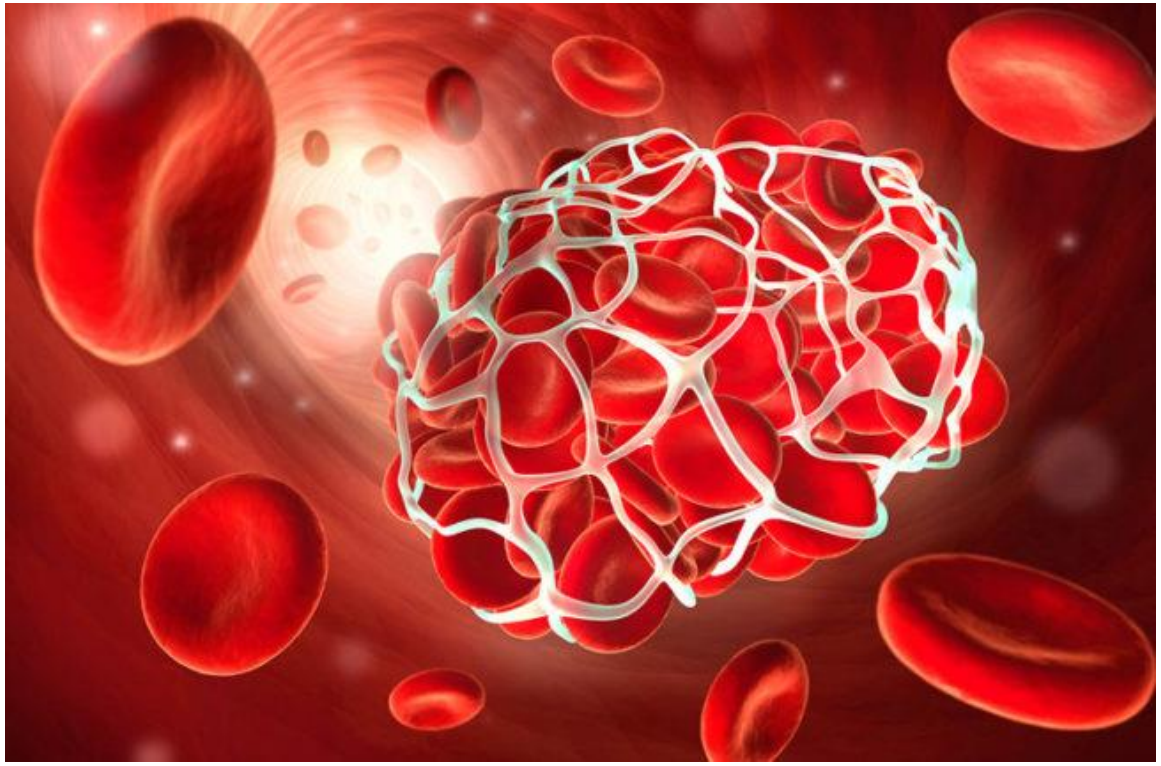
Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
1 /		Unknown				case series

2. Allele A is associated with decreased activity of DPYD.
The DPYD rs67376798 A allele was expressed in mammalian cells (HEK293 Flp-In) and protein expression and activity as compared to wild-type DPYD was analyzed. Cells with the A allele had significantly lower activity as compared to wild-type. Residual activity was 35%. However, when DPYD activity was assessed within a healthy cohort of 100 individuals (only one heterozygote was present in the population), there was only a tendency toward lower activity (p=0.6176). Please note alleles have been complemented to the plus chromosomal strand.
PMID:26804652 Annotation Page

Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
3 /		Unknown		< 0.001		cohort

PharmGKB
The Pharmacogenomics Knowledgebase

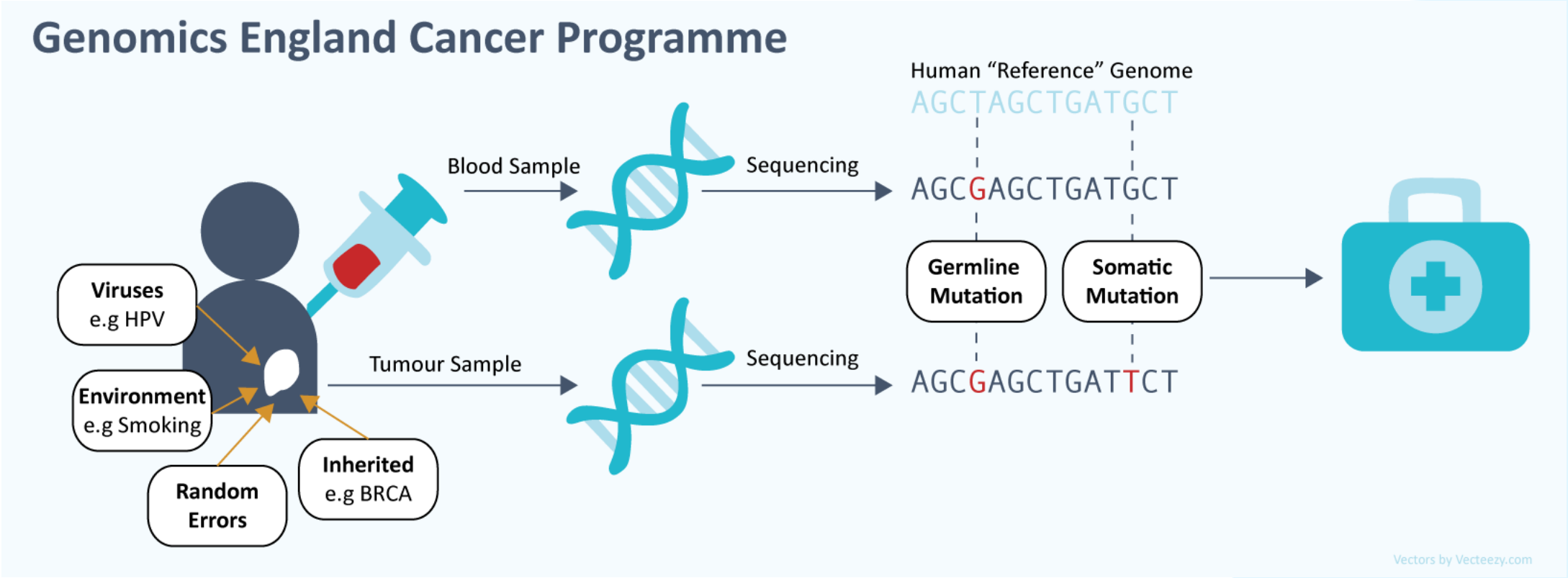
Фармакогенетика. Варфарин



Варфарин – антикоагулянт непрямого действия, угнетает активность свертывающей системы крови и препятствует образованию тромбов.

Гены CYP2C9, CYP4F2, VKORC1 влияют на дозировку

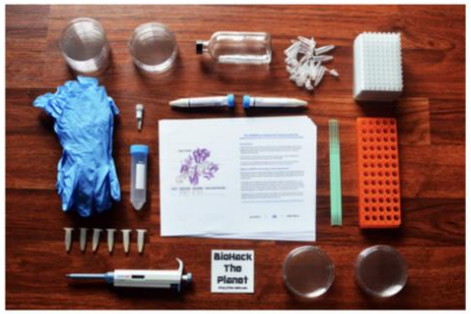
Онкогенетика



ГАТТАКА?

CRISPR

DIY Bacterial Gene Engineering CRISPR Kit



$159.00

Shipping: Calculated at checkout

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Product Description

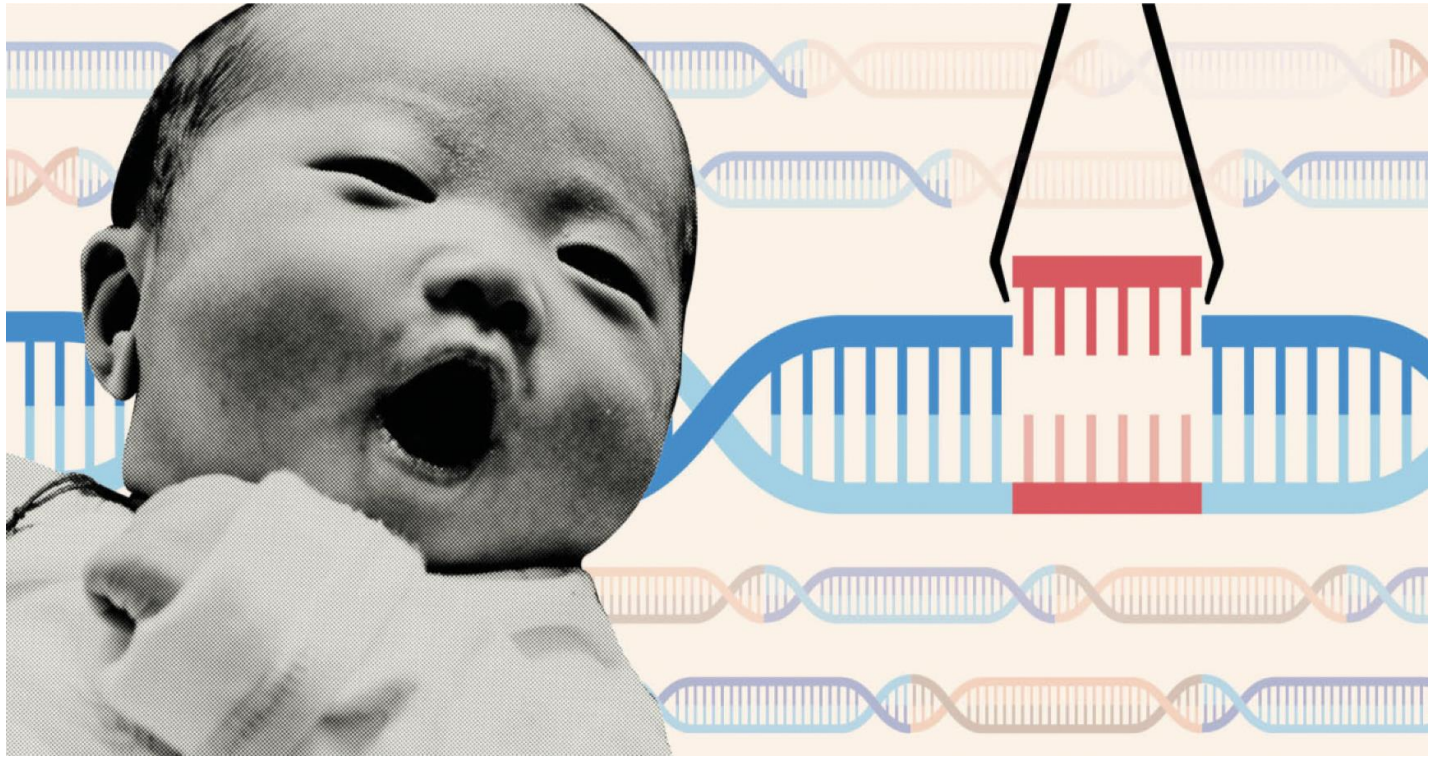
We ship 2-3 day, expect 5 business days for kit arrival but it will usually arrive faster.

Due to the overwhelming number of emails we will not respond to emails asking when your item will be shipped. Understand we are doing our best to get it to you.

Comes with an example experiment that teaches you many molecular biology and gene engineering techniques.

Want to really know what this whole CRISPR thing is about? Why it could revolutionize genetic engineering? This kit includes everything you need to make precision genome edits in bacteria at home including Cas9, tracrRNA, crRNA and Template DNA template for an example experiment.

Первые ГМО дети



Китайский ученый Хэ Цзянькуй применил технологию CRISPR для рождения двух детей с генетической защитой от ВИЧ

Он внес изменения в ген CCR5 (C-C-рецептор хемокина 5)

Одобренная FDA* генная терапия

FDA approval brings first gene therapy to the United States

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For Immediate Release: August 30, 2017

This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.

Español

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

***FDA – Foods and Drugs Administration, США**

Одобренная FDA* генная терапия

FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality

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For Immediate Release: May 24, 2019

The U.S. Food and Drug Administration today approved Zolgensma (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality.

"Today's approval marks another milestone in the transformational power of gene and cell therapies to treat a wide range of diseases," said Acting FDA Commissioner Ned Sharpless, M.D. "With each new approval, we see this exciting area of science continue to move beyond the concept phase into reality. The potential for gene therapy products to change the lives of those patients who may have faced a terminal condition, or worse, death, provides hope for the future. The FDA will continue to support the progress in this field by helping to expedite the development of products for unmet medical needs through the use of review pathways designed to advance innovative, safe and effective treatment options."

Стоимость генно-терапевтического препарата «Золгенсма» сразу после выпуска на рынок - 2 125 000 долларов США (порядка 170 000 000 рублей по текущему курсу).

***FDA – Foods and Drugs Administration, США**

eНано

Спасибо за внимание

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