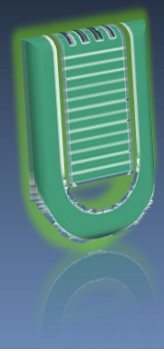
"Genetics and pharmacogenetics: implications for clinical practice "

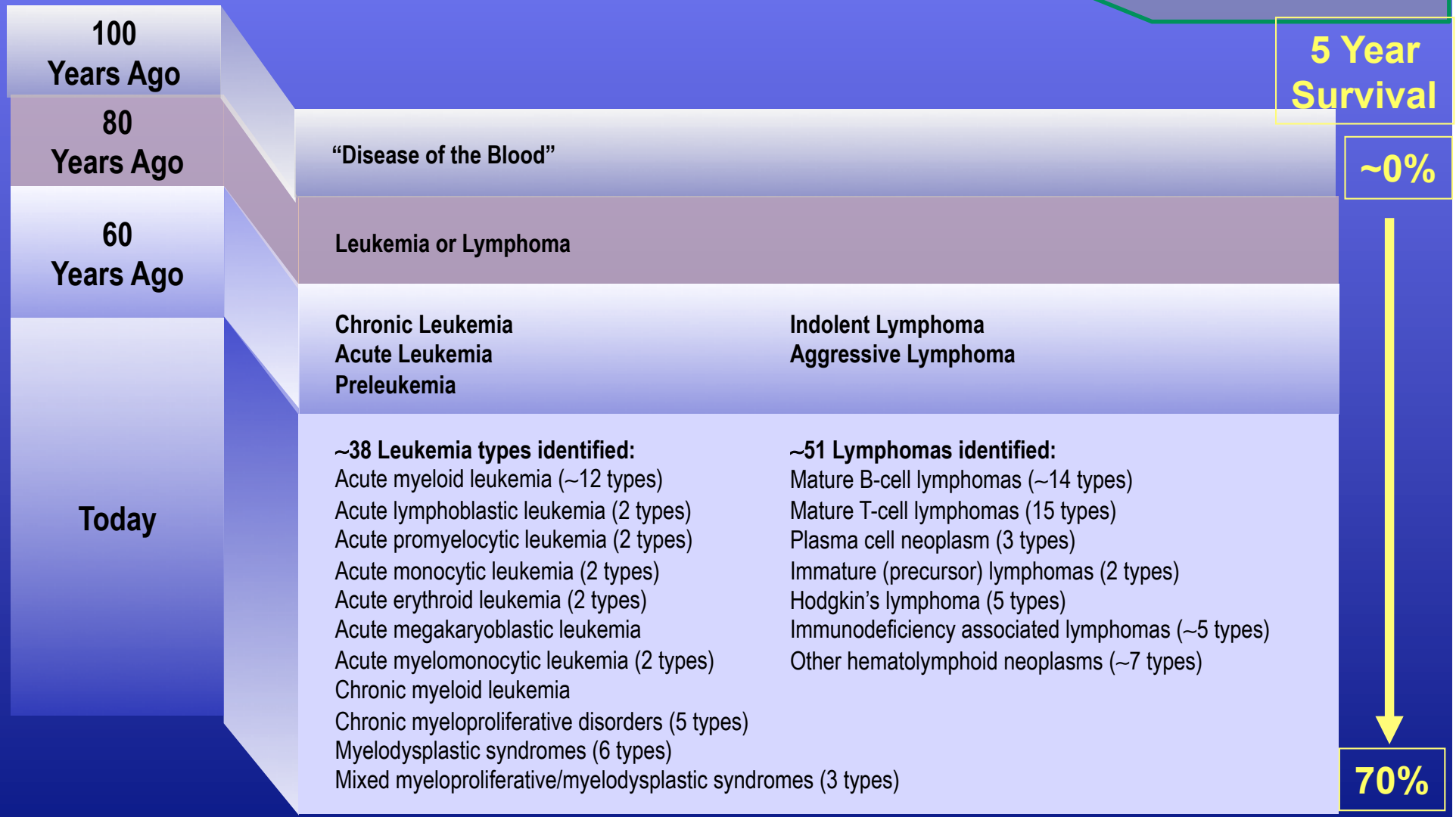
Giuseppe Novelli
novelli@med.uniroma2.it



CHMP/PGWP, London

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Positive Impact on Hematologic Cancers



Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (eds). *SEER Cancer Statistics Review*, 1975-2002, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on Nov 2004 SEER data submission, posted to the SEER web site 2005.

Slides prepared by Alison Lawton

“Girl, you’ve won the lottery”

PHARMACOGENOMICS

Playing the odds

Can doctors calculate a patient’s chance of being cured by searching their DNA? Hepatitis C researchers are starting to make this a reality.

BY AMY MAXMEN

“Girl, you’ve won the lottery,” said Deborah Teeters’ doctor, when the results of her genetic test came back revealing two Cs at a spot among the 3 billion base pairs of her genome. Teeters, a retired child-welfare reform worker in North Carolina, had avoided treatment for hepatitis C for more than a decade because of its ugly side effects, including anaemia, fevers and severe depression. She also knew that for roughly half of all patients the 48-week regimen doesn’t work. But two Cs means the odds are in her favour. She is ready to give it a shot.

Hidden within the scratch card of our genomes lie clues to how each individual uniquely responds to stress, disease and medication. If single ‘letter’ variations, called single nucleotide polymorphisms (SNPs), with high

everyone inherits one *IL28B* gene from each parent, there are three possible combinations: CC, CT and TT. Patients with two Cs tend to clear the hepatitis C virus (HCV) when treated, whereas a CT or a TT genotype correlates with a poorer response (see ‘Lucky Cs,’).

A test for this SNP now helps patients decide whether to undergo treatment — which currently consists of a year-long course of interferon-α injections plus multiple daily oral doses of ribavirin — or to wait until improved drugs hit the market. And pharmaceutical companies are interested in using the test to tailor their new drugs to specific populations. In this way, hepatitis C is a success story among those who use genome-wide association studies (GWAS) to search the genome for SNPs that are clinically relevant.

“*IL28B* was a fantastic hit because nothing had ever proved as useful in GWAS before,” but nothing else I know of has been put to use in the clinic and in clinical trials.”

It’s been a whirlwind journey. *IL28B* SNPs were first linked to treatment response in late 2009 (refs 1–3) — less than a year later, doctors and pharmaceutical companies were ordering *IL28B* SNP tests. Based on the C/T SNP1, the first test was offered for about US$150 in July 2010, by LabCorp, a diagnostics company based in Burlington, North Carolina. Since then, “the test has been going gangbusters,” says John McHutchison, a co-author of one of the *IL28B* papers[1] who is now at biopharmaceutical company Gilead Sciences (Foster City, California). Indeed, in April 2011, another company, Quest Diagnostics (Madison, New Jersey), launched its own version of the test.

For the majority of HCV infections in the West, the *IL28B* SNP is a more accurate predictor, or biomarker, of an individual’s response

ILLUSTRATION BY SOPHIE CASSON/THEDNABOX.COM

Genomic Biomarker Definition

- **A Genomic Biomarker is Defined as:**

  A Measurable DNA or RNA Characteristic that is an Indicator of Normal Biologic Processes, Pathogenic Processes, and/or Response to Therapeutic or other Intervention.

Defining Attributes of Genomic Biomarkers

- A genomic biomarker could, for example, reflect:
  - the regulation of a gene
  - the expression of a gene
  - the function of a gene

- A genomic biomarker does not expand into:
  - Proteomics
  - Metabolomics

DNA characteristics include, but are not limited to:

- Single nucleotide polymorphisms (SNPs)
- Variability of short sequence repeats
- DNA modification, e.g. methylation
- Insertions
- Deletions
- Copy number variation
- Cytogenetic rearrangements, e.g. translocations, duplications, deletions or inversions

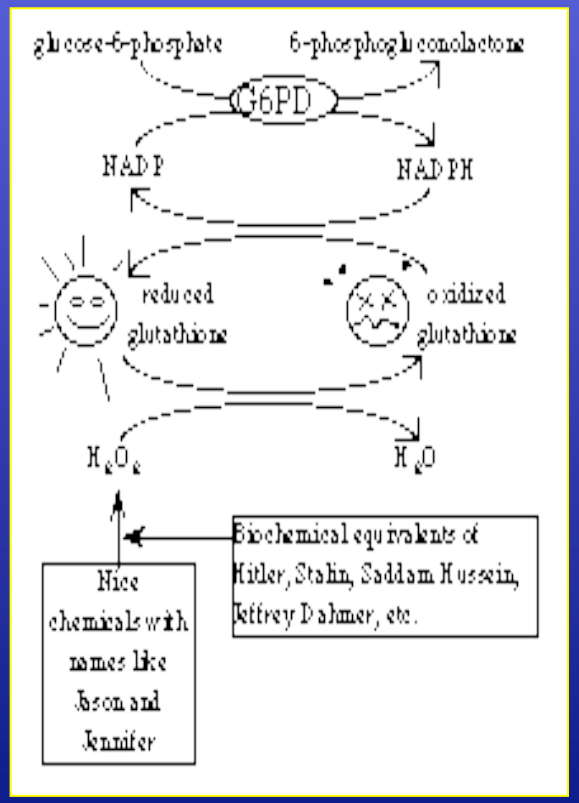
RNA characteristics include, but are not limited to:

- RNA sequence
- RNA expression levels
- RNA processing, e.g. splicing and editing
- **MicroRNA levels/types**
- **mRNA Pseudogenes** (ceRNAs)

A genomic biomarker may be used to assess or detect:

- A specific disease as early as possible – diagnostic biomarker (HCV RNA after infection)
- The risk of developing a disease – susceptibility/risk biomarker (BRCA1-breast cancer)
- The evolution of a disease (indolent vs. aggressive) – prognostic biomarker (HER-2-breast cancer) – but it can be predictive too
- The response and the toxicity to a given treatment – predictive biomarker (EGFRNSCLC/gefitinib, DPD-gastrointestinal cancer/fluoropyrimidines)

Genetic factors involved in drug effects



G6PD deficiency favism association

Pharmacogenomics and Pharmacogenetics Definitions

- **Pharmacogenomics (PGx) is defined as the investigation of variations of DNA and RNA characteristics as related to drug response.**

- **Pharmacogenetics (PGt) is a subset of PGx and is defined as the influence of variations in DNA sequence on drug response.**

  - PGx and PGt are applicable to activities such as drug discovery, drug development, and clinical practice.
  - Drug response includes drug disposition (PK) and drug effect (PD).

How does EMA support

Biomarkers/Pharmacogenomics/personalised Med

1) **Dedicated Biomarker qualification procedure**
2) **Development of regulatory guidance**
3) **Scientific advice process**
   - **Through SWAP, PGxWP, ATMP**
4) **Innovation task force meetings**
   - *(http://www.emea.europa.eu/htms/human/mes/itf.htm)*
5) **Regulatory support to projects in the Innovative Medicines Initiative (IMI) and Critical Path**

   (eg Joint EMEA/FDA VXDS)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MHRA

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. EMEA/CHMP/SAWP/72894/2008 Corr[1]

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS

DRAFT AGREED BY SAWP	27 February 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2008
FINAL AGREED BY CHMP	22 January 2009

KEYWORDS	*EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.*

EMA & Regulatory Guidelines

1) Dedicated Biomarker qualification procedure

2) **Development of regulatory guidance**

- Reflection paper on co development of Pg BM and assays for drug development (comments received November 2010)
- Reflection paper on methodological issues associated with PG biomarkers (Released for consultation)
- Reflection paper on genomics and personalised medicines (Release for consultation due 1th Q'11)

3) Regulatory support to projects in the Innovative Medicines Initiative (IMI) and Critical Path

(eg Joint EMEA/FDA VXDS on BM nephrotoxicity)

Strategic use of Genomic Biomarkers in clinical development

- **Use Genomic Biomarker for:**
  - Better definition of disease
  - Dose adjustments
  - Stratify to distinguish responders from non-responders
  - Stratify to exclude patients at risk for AE
  - Enrichment of responder population
  - "Rescue" trials with pre-defined subgroup analyses
- **Get:**
  - More informed development process
  - Faster
  - …better B/R and more chance of success


TAKE TWO GENES AND CALL ME IN THE MORNING.
grimmy.com

Phenotype

- 1. Different Genes/Mutations
- 2. Different Populations
- 3. Individual “genometype”
- 4. Different Environments

Validation and biomarker qualification

"establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a biomarker that meets its pre-determined specifications and quality attributes”

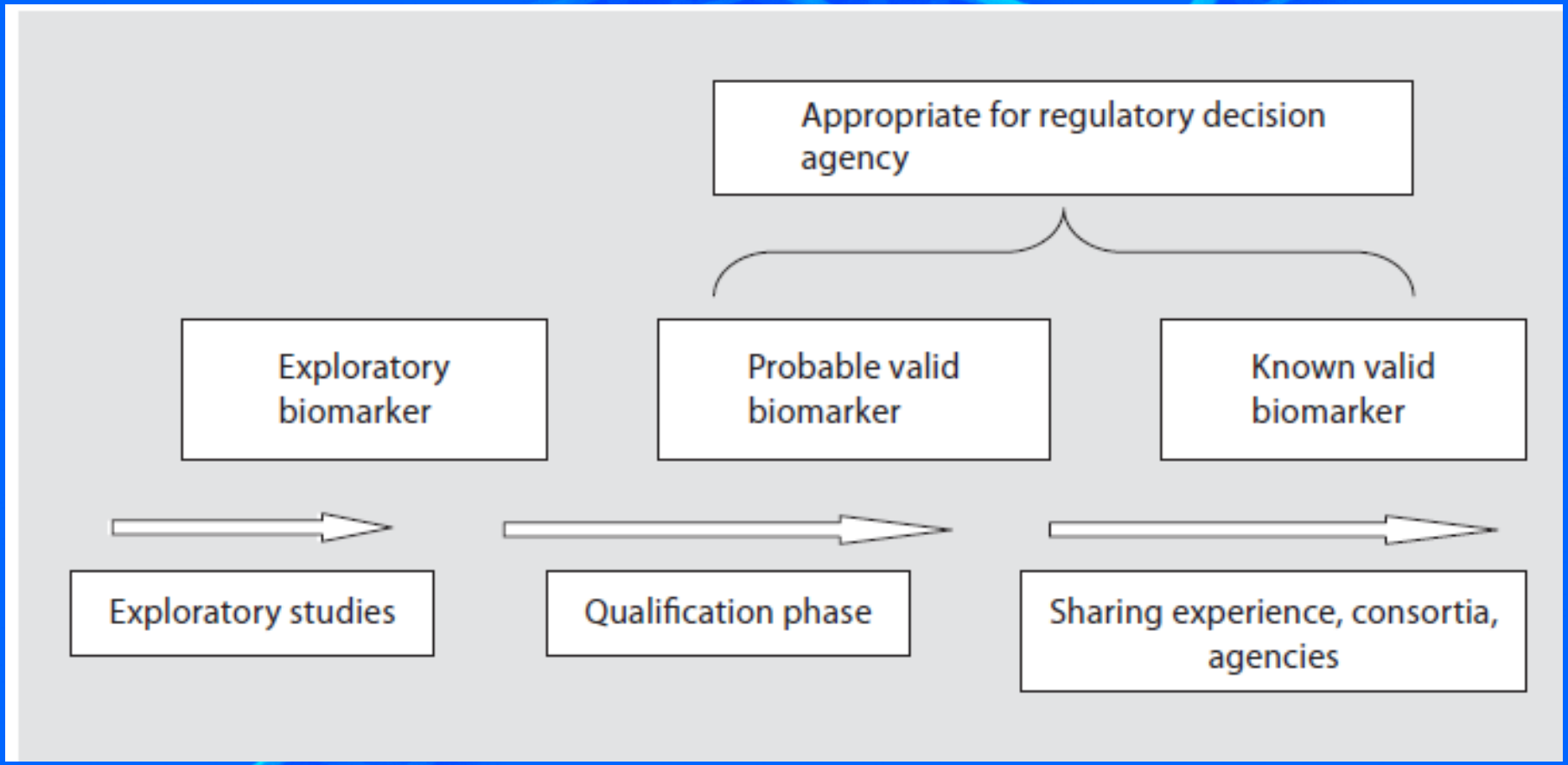
Qualification is defined as

"a conclusion that the biomarker data submitted support use of the biomarker in drug discovery, drug development or post approval studies and where appropriate, in regulatory decision making"

EMA process for the biomarker qualification

- High analytical validity
- Appropriate sensitivity and specificity
- Clinical validity/ Clinical utility
- Ability to influence treatment plan
- Possibly free of environmental & clinical factors

HOW?



Novelli et al., 2009

There is no guide line on What exactly is qualification !

- Fit for purpose; (*predictive, prognostic surrogate)*
- Requirements may differ based on :
  - BM linked to a medicine or not
  - With the therapeutic field
  - Timing of assay development
- ”Clinical validity” different from ” Clinical utility”, although both are not independent concepts !

Clinical Utility:
the bridge to post-approval development

EUROPEAN MEDICINES AGENCY

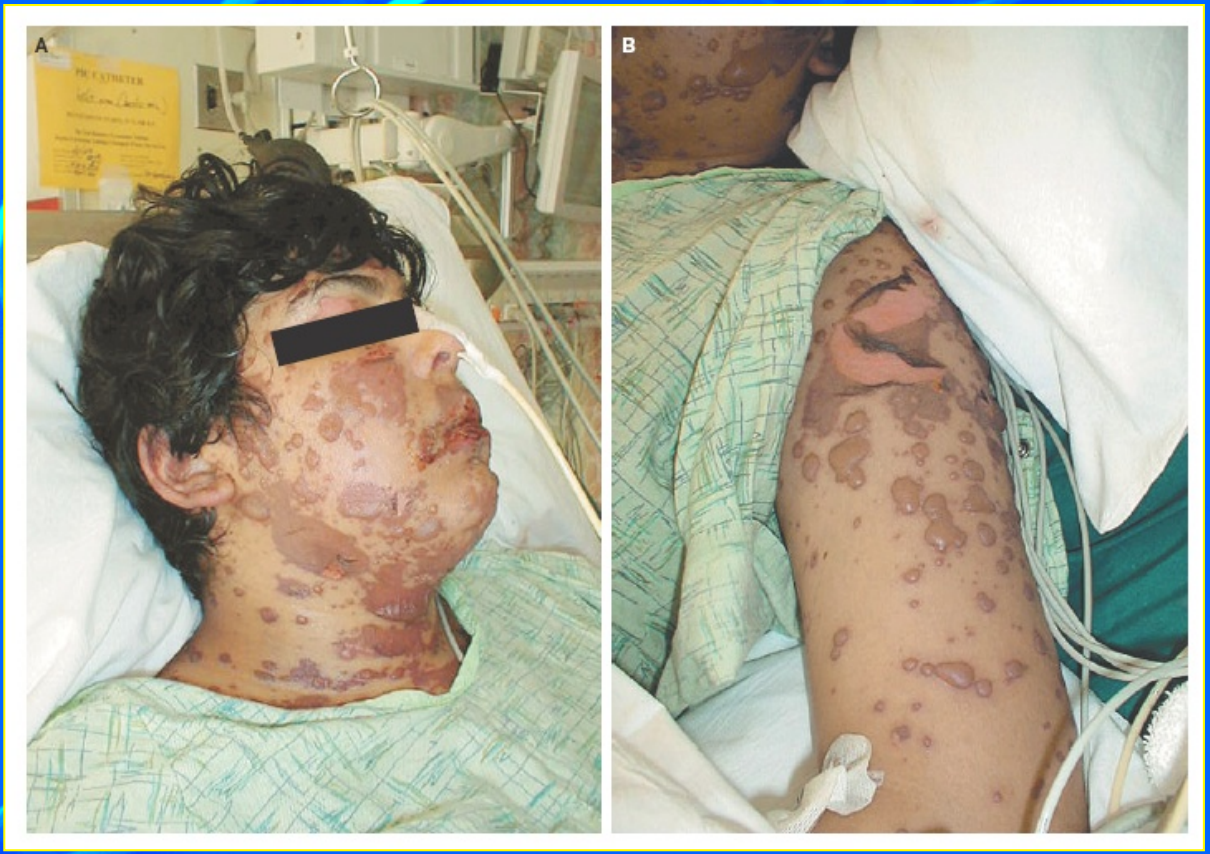
For the medicines Regulator: Risk/Benefit of therapy in the lifecycle (not all the story complete at MAA....)

- With a positive test/with a negative test/without a test
- Impact of false positives/false negatives
- Ethnicity and genotype variants

For the HTA Regulator

- How the test impacts on current practice
- Which would be the gain
- Is the test available and affordable
- IVD versus homebrew

Stevens–Johnson Syndrome



carbamazepine (CBZ), lamotrigine (LTG), phenobarbital (PHB), phenytoin (PHT), or valproic acid (VPA)

- 2008 - PhVWP and PgWP discussions on the strong association between HLA-B*1502 and CBZ-induced SJS in subjects of Han Chinese or Thai origin,
  - agreed to update SPC of carbamazepine: sections 4.2 and 4.4

- 2009 - A similar assessment on phenytoin-related SJS and HLA-B*1502 in subjects of Han Chinese or Thai origin
  - SPC update in section 4.4

Phenytoin (for oral administration) SPC 4.4

- "HLA-B*1502 may be associated with an increased risk of developing Stevens-Johnson syndrome (SJS) in individuals of Thai and Han Chinese origin when treated with phenytoin. If these patients are known to be positive for HLA-B*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

- In the Caucasian and Japanese population, the frequency of the HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available."

HLA-A*3101 and CBZ-Induced Hypersensitivity Reactions in Japanese

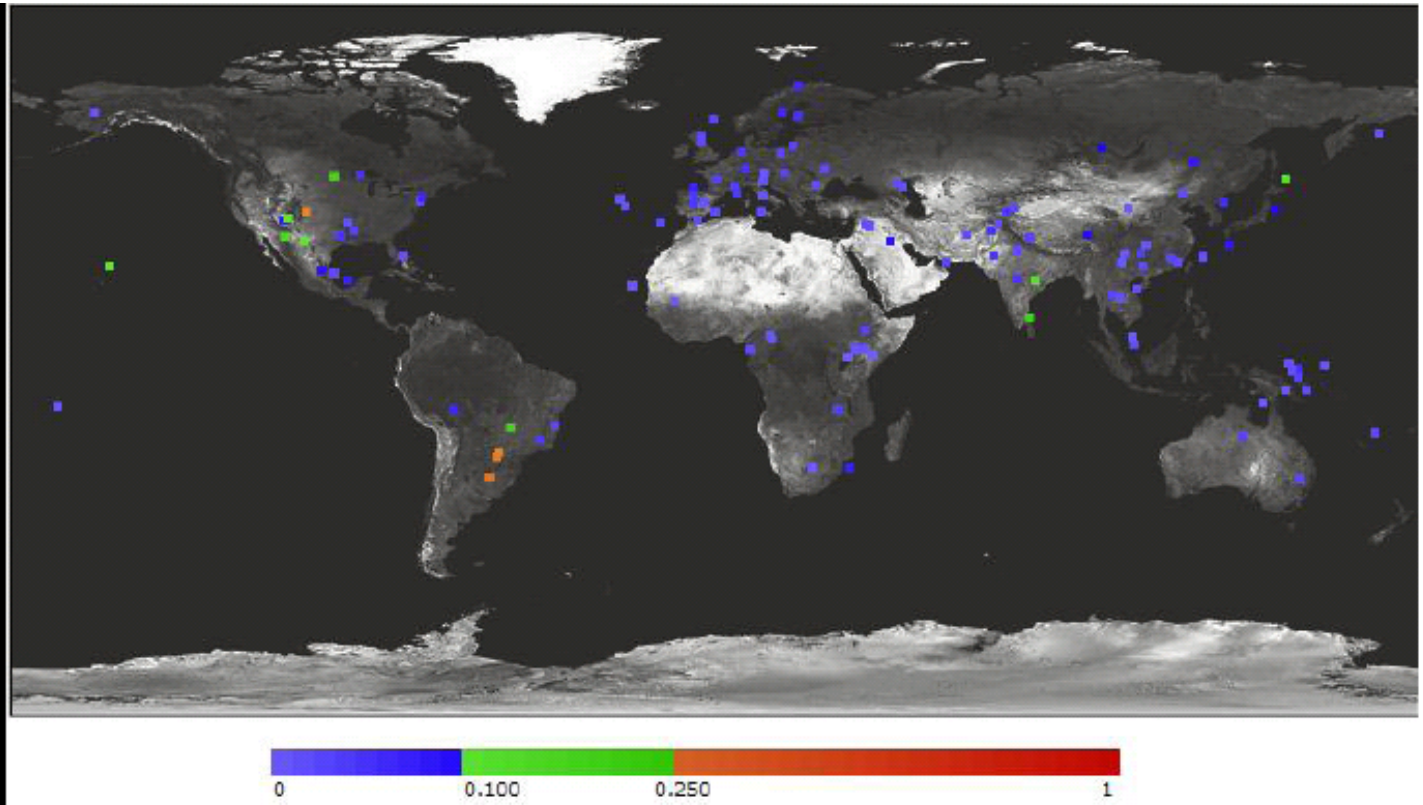
- GWAS was conducted in 53 subjects with CBZ-induced cADRs, including SJS, TEN and hypersensitivity syndrome (DIHS), and 882 subjects of a general population in Japan.
- 12 SNPs showed significant association and rs1633021 showed smallest P-value ($P = 1.18 \times 10^{-13}$). These SNPs location including the HLA-A locus.
- HLA-A alleles were genotyped in 61 cases and 376 CBZ-tolerant controls. A*3101 present in 60.7% (37/61) of the cases, only 12.5% (47/376) of the controls (OR= 10.8, 95% CI 5.9–19.6, $P = 3.64 \times 10^{-15}$).
- sensitivity 60.7% and specificity 87.5% for CBZ-induced cADRs.
- If a prevalence of CBZ-induced cADRs was 2.9%, the PPV would be 12.7 and NPV 98.7%.
- It might be possible to lower the frequency of CBZ-induced cADR from 2.9 to 1.1% by excluding HLA-A*3101 carriers from CBZ treatment.

HLA-A*3101 and CBZ-Induced Hypersensitivity Reactions in Europeans

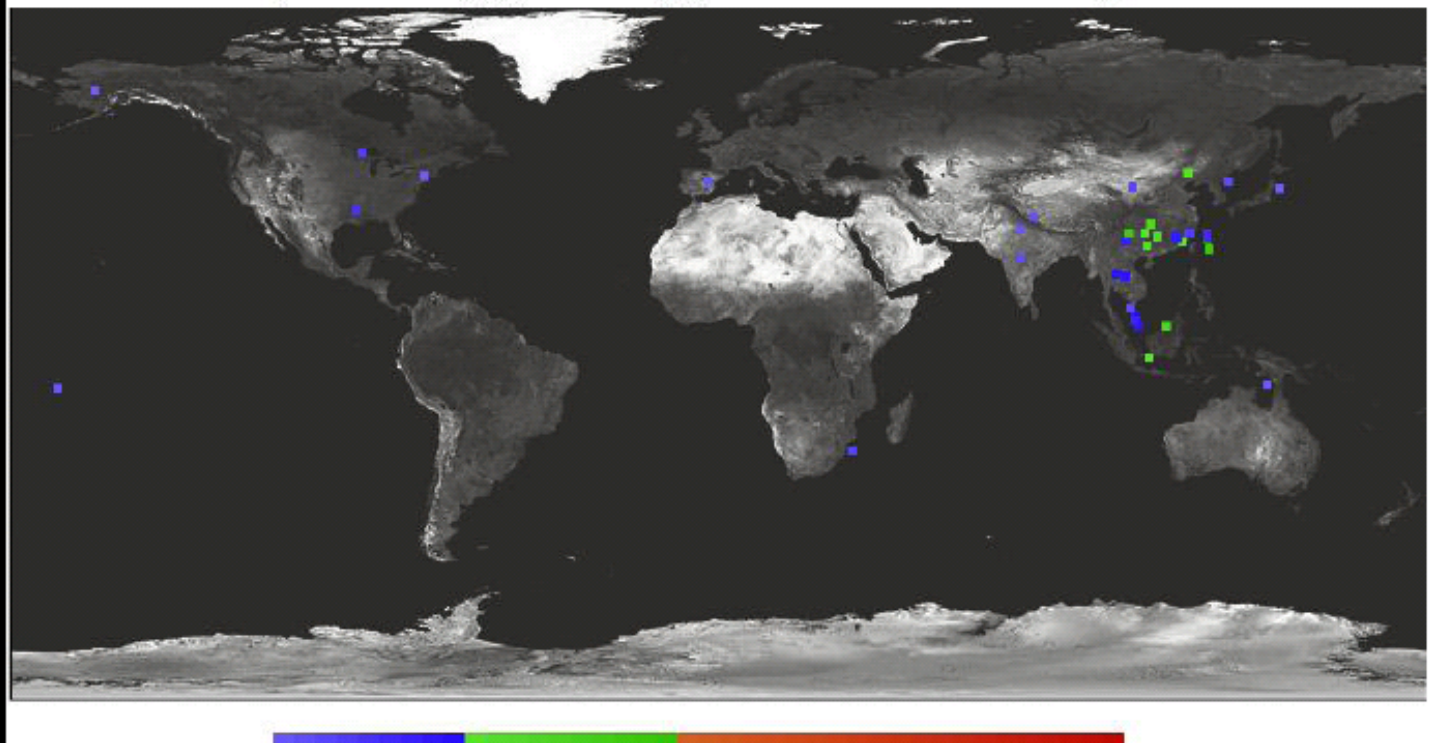
- GWAS was conducted in 22 cases of CBZ-induced hypersensitivity syndrome, 43 subjects with CBZ-induced maculopapular exanthema, and 3987 control subjects, all of European descent.
- The associations were replicated in 145 subjects with CBZ-induced hypersensitivity reactions.
- Follow-up genotyping confirmed the variant as a risk factor for
  - **hypersensitivity syndrome (OR, 12.4; 95% CI, 1.27 to 121), 10/27**
  - **maculopapular exanthema (OR, 8.33; 95% CI, 3.59 to 19.36), 23/106**
  - **SJS–TEN (OR, 25.9; 95% CI, 4.93 to 116). 5/12**
- A*3101 allele has a prevalence of 2 to 5% in Northern Europeans
- The presence of the allele increased the risk from 5.0% to 26.0%, whereas its absence reduced the risk from 5.0% to 3.8%.

Genetic markers in difference ethnic populations for different carbamazepine induced cutaneous ADRs - Example on how information can be presented in SPC

	HLA-B*1502	HLA-A*3101
Han Chines and Thai	Screening recommended: when ever possible, to prevent CBZ induced SJS (see 4.2)	For information:This GBM is associated with maculopapular exanthema (and not SJS) in Han Chinese (see 5.1).
Other Asian populations than Han Chines/Thai or Japanese (e.g. Malaysian and Indian (Hindu))	Testing recommended: possible to reduce the CMZ incuded SJS (see 4.4)	No information.
European Caucasians and Japanese	Testing not recommended. No association between this GBM and CBZ induced SJS (see 4.4) .	Testing recommended: possible to reduce the CMZ incuded hypersensitivity reactions. (see 4.4)



- HLA-A*3101 worldwide distribution



- HLA-B*1502 worldwide distribution

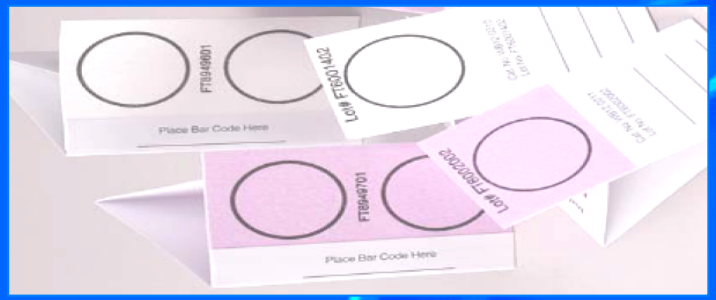
www.allelefrequencies.net

ABACAVIR Hypersensitivity

- Approximately 5% of patients in clinical trials
- Onset
  - symptoms usually appear within first 2 weeks; rare >6wks
  - May occur at any time and worsen during therapy
  - Usually resolve quickly upon discontinuation
- Symptoms
  - Frequently fever +/- fatigue, or N/V/D, abdominal pain. Rash may or may not be present
  - 20% of patients will also have various respiratory symptoms
  - Multiorgan/body system involvement

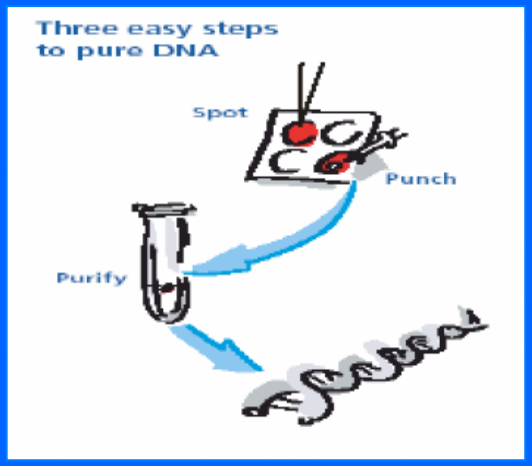
- HLA-B*5701 genetic screening to predict HSR to Abacavir

Abacavir testing by regular mail

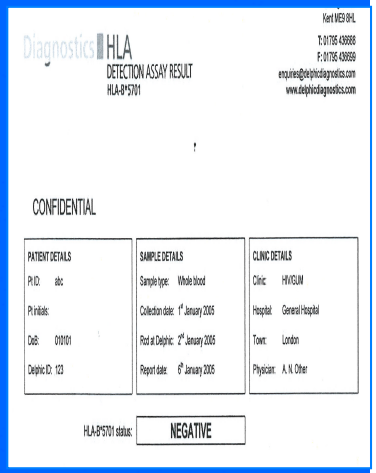


campioni raccolti su carta FTA, conservati a temperatura ambiente

spediti per posta



analisi



referto

Campioni spediti per posta

Screening HLA-B*5701: quanto viene impiegato in Italia?

Trend di impiego dello screening per HLA-B*5701 in Italia (ottobre 2007- agosto 2009)

Genomic BMs, scope of inclusion in labelling.

Product	INN name	Biomarker	Scope
Ziagen	abacavir	HLA-B*5701	Safety
Herceptin	trastuzumab	HER2 receptor	Efficacy
Glivec	imatinib	c-kit	Efficacy
Trisenox	Arsenic trioxide	PML/RARa	Efficacy
Erbitux	cetuximab	EGFR/K-Ras	Efficacy
Tarceva	erlotinib	EGFR	Efficacy
Sprycel	dasatinib	PH+ Chromosome	Efficacy
Celsentri	maraviroc	CCR5 coreceptor	Efficacy
Tasigna	nilotinib	PH+ Chromosome	Efficacy
Vectibix	panitumumab	K-Ras	Efficacy
Tyverb	lapatinib	HER2	Efficacy
Iressa	gefitinib	EGFR	Efficacy
Multiple tradenames	carbamazepine	HLA-B*1502 HLA-A*3101	Safety
Multiple tradenames	Phenytoin	HLA-B*1502	Safety
Multiple tradenames	Tamoxifen	CYP2D6	Efficacy- Interactions
Multiple tradenames	Clopidogrel	CYP2C19	Efficacy
Abilify	aripiprazole	CYP2D6	Safety
Xeloda	capecitabine	DPD	Safety
Onsenal[#]	celecoxib[#]	CYP2C9	Safety
Faslodex	fulvestrant	Estrogen receptor	Efficacy
Viracept	nelfinavir	CYP2C19	Safety
Fasteurtec	rasburicase	G6PD	Safety

James Watson; Living with my personal genome

FSG Newsletter, November 2009

"I am homozygous for the “10” variant of the P450 drug metabolizing gene, *CYP2P6* . As a result, I metabolize beta-blockers much more slowly than most other Caucasians. Before I take this knowledge, my use of beta-blockers to control my blood pressure caused me to constantly fall asleep at inappropriate moments. Instead of a daily pill, I now take one every week”….