



Rules & Algorithms, Derivation, Deviation and Validation

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“Rules & algorithms, derivation, deviation & validation”

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Rules & Algorithms for Interpreting Genotypic Resistance Assay Results

- Scientific basis
- How they are derived
- Limitations
- Comparisons
- Validation

Three Pillars of the Genotypic World



Mutation

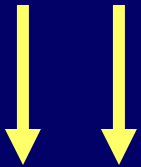
The diagram consists of three light blue circles with thin yellow borders, arranged in a triangular pattern. The top circle is labeled 'Mutation', the bottom-left circle is labeled 'Drug', and the bottom-right circle is labeled 'Response'. The circles are set against a dark blue background.

Drug

Response

Mutation, Drug and Response

Mutation Drug



Response



Clinically Relevant Interpretation of Resistance Assay Results

*“if you have this mutation and you receive this
drug, this will be your response”*

Multiple Factors Complicate Association

“Mutation”

Combination of mutations
Mutations to other targets
Undetected mutations

“Drug”

Combination of drugs
Drugs switched
before response measured
Adherence to drugs
PK of drugs

“Response”

VL, CD4, Clinical
Does short VL = clinical
How late VL needed

Clinically Relevant Interpretation of Resistance Assay Results

*“if you have these mutation and you receive
this drug as part of your regimen, it will
contribute this much to your virological
response”*

Scientific basis for determining affect of genotypic changes on drug resistance

- Genotype to phenotype
- Genotypic changes associated with specific drug therapy
 - in vitro selection
 - in vivo selection (patients failing)
- Genotype to virological response
- Genotype to clinical outcome

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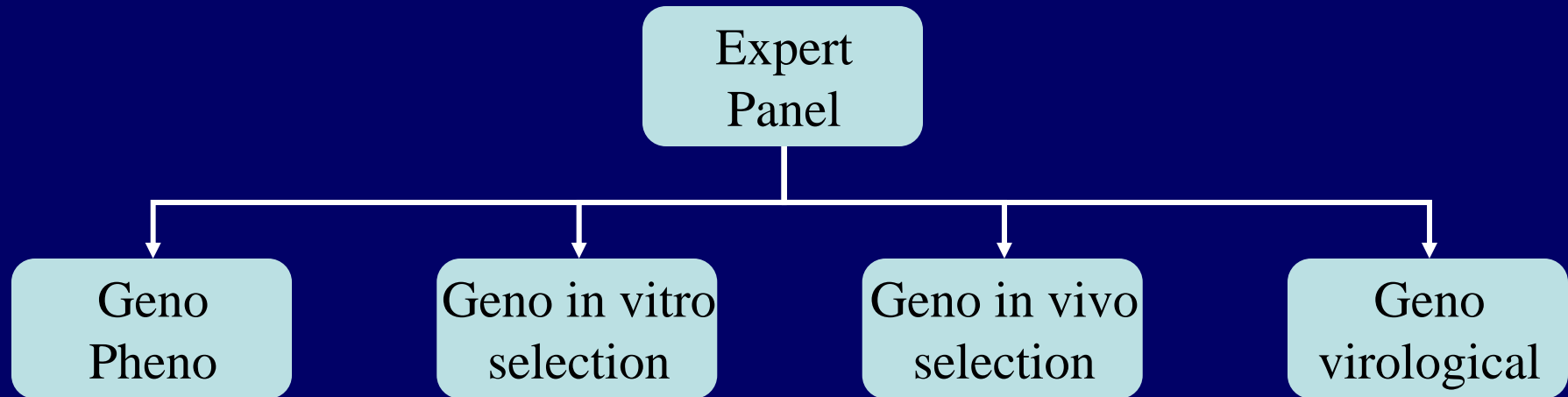


Deriving Rules and Algorithms

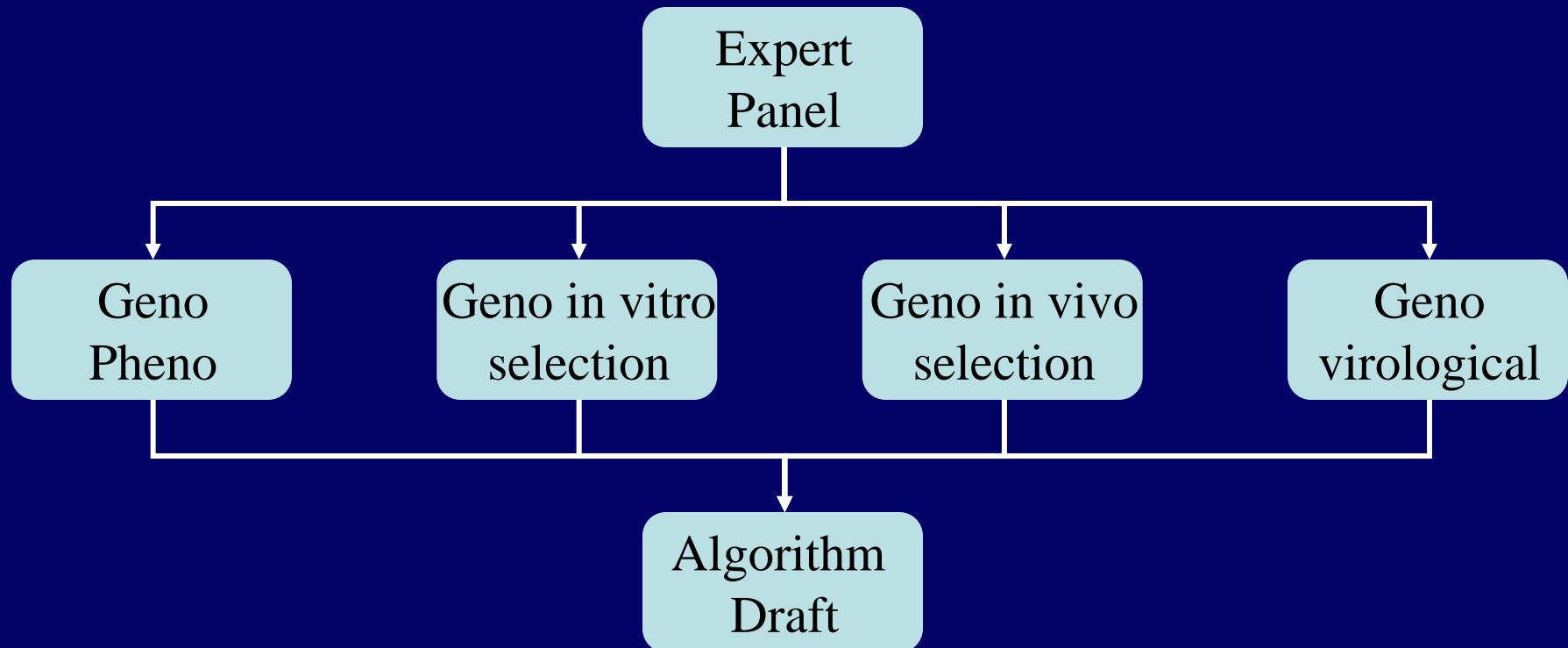
Deriving Rules and Algorithms

Expert
Panel

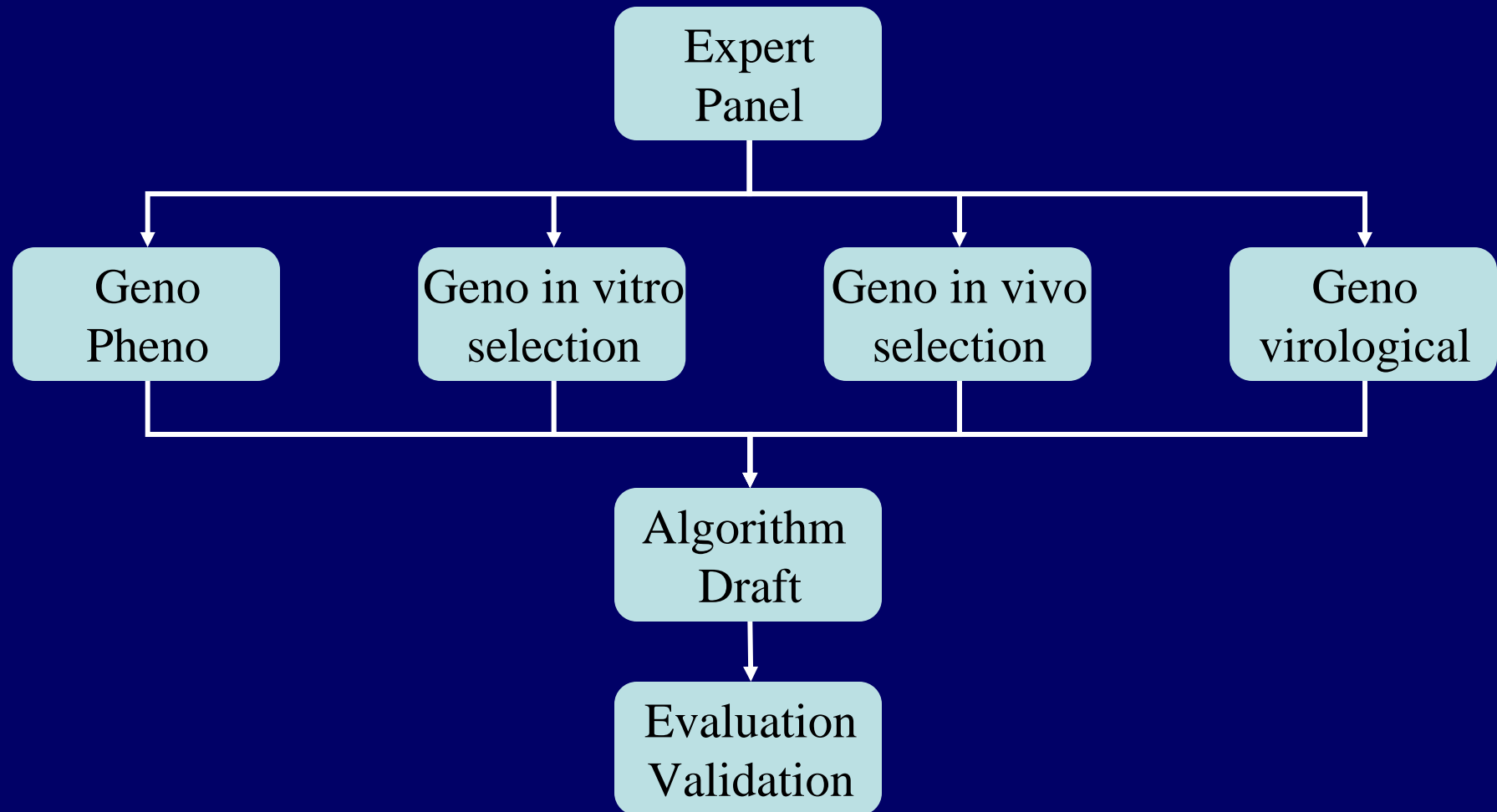
Deriving Rules and Algorithms



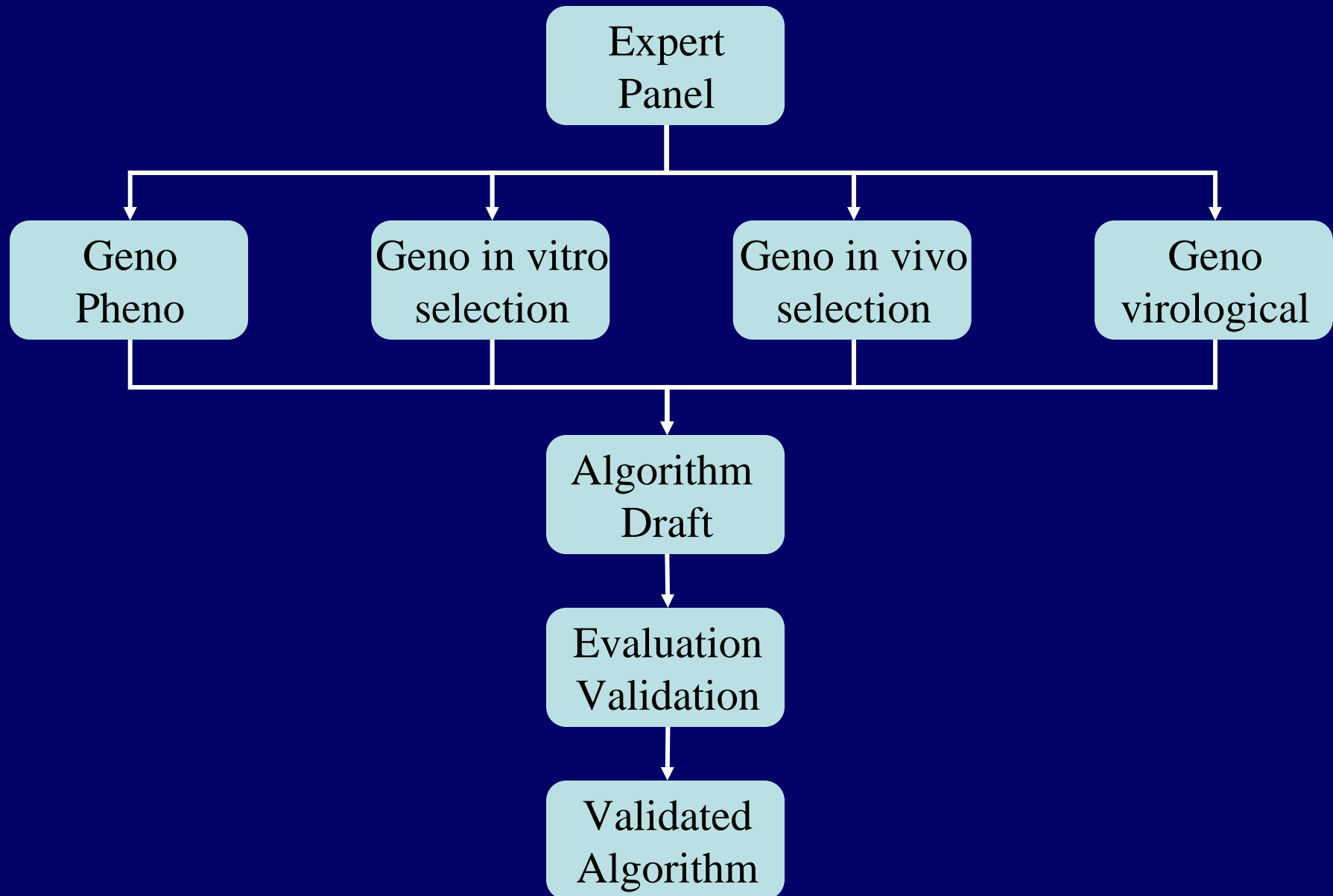
Deriving Rules and Algorithms



Deriving Rules and Algorithms



Deriving Rules and Algorithms



Limitations – Expert Panel

- **Qualifications** (*you're an expert? – says who?!*)
- **Number of panel members**
- **Rotation**
- **Bias** (*MY data are bigger than YOUR data*)

Limitations - Data

- Quality and amount of data varies greatly between drugs
 - How long has the drug been available
 - How intensely was it studied
- Quality and amount of data varies greatly between mutations
 - Prevalence of mutation (subtypes?)
 - Selection by drug used previously (e.g. protease L90M)

Limitations – Evaluation and Validation

- How do we correctly compare algorithms?
- What constitutes proper validation?

5th International Resistance workshop, Scottsdale, 2001
Schapiro et al, EuroGuidelines Group for HIV Resistance

Table 1: List of 19 genotypic resistance interpretation systems initially identified

1. Mutation list by the International AIDS Society (Hirsch et al., 2000) <http://hivinsite.ucsf.edu/>
2. Mutation list included in the French guidelines (http://www.sante.gouv.fr/htm/actu/36_vih_2.htm)
3. Mutation list included in the guidelines by the US Dept of Health and Human Services (<http://www.hivatis.org>)
4. Mutation list included in the British Guidelines (<http://www.aidsmap.com/>)
5. Scoring system of the HIV Resistance Collaborative Group (<http://www.logicarepartners.com>)
6. Schinazi website table (Schinazi et al., 2000; <http://www.viro.com>)
7. Los Alamos website - <http://hiv.web.lanl.gov/>
8. Stanford website database (Shafer et al., 1999; <http://hivdb.stanford.edu>)
9. Viradapt genotypic algorithm (Durant et al, 1999)
10. Menéndez genotypic algorithm (Clotet et al, 2000, section 5 algorithm 1)
11. Rega Institute specific genotypic algorithm (Vandamme et al, vandamme@uz.kuleuven.ac.be)
12. Retrogram stand alone software based on specific genotyping algorithms (great@vironet.com)
13. Virtual Phenotype (Commercial interpretation system, www.vicolab.com)
14. TruGene kit interpretation system (Visible Genetics, www.visgen.com)
15. HIVresistanceWeb: <http://www.hivresistanceweb.com/protected/mutationtables/pi.shtml>
16. Database tool of the National Public Health Institute, Helsinki, Finland. (Salminen et al, 2001)
17. "geno2pheno" (Phenotype prediction from genotypic/phenotypic database. <http://cartan.gmd.de/geno2pheno.html>)
18. HIV TherapyEdge. bmccreedy@therapyexpert.com
19. HIV GenotypR PLUS, Specialty <www.specialtylabs.com>

5th International Resistance workshop, Scottsdale, 2001
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- Q/A Validation of Software

Reported using US/Euro Q/A standards 4

In progress 2

No validation 2

Not stated 3

No Software 6

- Clinical Validation

Yes or partial 6

No 10

Not Stated 1

2006: Genotypic Interpretation Systems

- > 20 systems (depending on definition)
- Majority Rules based algorithms
- Minority Geno to Pheno database correlations
- No formal registrar or collaborative working group

Publicly available systems for genotypic resistance interpretation

Adapted from: *Lui & Shafer, Web resources for HIV type 1 genotypic-resistance test interpretation. Clin Infect Dis. 2006 Jun 1;42(11):1608-18*

<u>Name</u>	<u>URL</u>
HIVRT&PrDB Stanford University	http://hivdb.stanford.edu
ANRS France	http://www.hivfrenchresistance.org
Rega Institute Belgium	http://www.kuleuven.be/rega
Antiretroscan, ARCA Italy	https://www.hivarca.net
Geno2pheno Germany	http://www.Geno2pheno.org

Commercial drug resistance interpretations

Adapted from: *Lui & Shafer, Web resources for HIV type 1 genotypic-resistance test interpretation. Clin Infect Dis. 2006 Jun 1;42(11):1608-18*

Name	URL
Monogram Biosciences(South San Francisco, CA, U.S.)	http://www.virologichiv.com/assays/hcp/geneSeqHIV.aspx
Virco Laboratories (Mechelin, Belgium)	http://www.vircolab.com
ViroSeq (Celera Diagnostics / Abbott Laboratories)	http://www.celeradiagnostics.com/cdx/ViroSeq
TruGene HIV-1 (Bayer Diagnostics)	http://www.labnews.de/en/products/pr_truso.php
PhenoScript (Viralliance)	http://www.viralliance.com/html/company.html
Advanced Biological Laboratories (ABL, Luxembourg)	http://www.therapyedge.com/site/en/product_vs.html

Comparisons of Rules and Algorithms

- DeLuca et al. *Variable prediction of antiretroviral treatment outcome by different systems for interpreting genotypic human immunodeficiency virus type 1 drug resistance* J Infect Dis. 2003 Jun 15;187(12):1934-43
- DeLuca et al. *Variability in the interpretation of transmitted genotypic HIV-1 drug resistance and prediction of virological outcomes of the initial HAART by distinct systems.* Antivir Ther. 2004 Oct;9(5):743-52.
- Snoeck et al. *Discordances between interpretation algorithms for genotypic resistance to protease and reverse transcriptase inhibitors of human immunodeficiency virus are subtype dependent.* Antimicrob Agents Chemother. 2006 Feb;50(2):694-701.

Comparisons of Rules and Algorithms

- Ravela et al. *HIV-1 protease and reverse transcriptase mutation patterns responsible for discordances between genotypic drug resistance interpretation algorithms*. J Acquir Immune Defic Syndr. 2003 May 1;33(1):8-14.
- Costagliola et al. *Initiatives for developing and comparing genotype interpretation systems step1: External validation of existing rules-based algorithms for abacavir and ddI evaluated on virological response*. Antiviral Therapy 2005, 10: S11

Comparisons of Rules and Algorithms

- Assess the concordance of algorithm interpretations
- Four algorithms compared:
 - ANRS
 - Stanford HIVDB
 - Rega Institute
 - Visible Genetics Inc
- Sequences of isolates from 2,045 individuals applied to each algorithm
- Drug resistance interpretations were classified as
 - S for susceptible
 - I for intermediate
 - R for resistant

Comparisons of Rules and Algorithms

30,675 interpretations (2,045 sequences x 15 drugs):

- 4.4% were completely discordant, with at least one algorithm assigning an S and another an R
- 29.2% were partially discordant, with at least one algorithm assigning an S and another an I, or at least one algorithm assigning an I and another an R
- 66.4% displayed complete concordance

Comparisons of Rules and Algorithms

- Interpretation systems compared in their ability to predict virological response to ddI and abacavir
- Considerable variability in predicting resistance
 - Abacavir: 7.3 – 31.9%
 - ddI: 8.0% - 13.5%
- Poor correlations for between change in viral load and sensitivity for many systems
- Important of external validation of rules

Genotypic interpretation systems*

System	Method	Updated	Referenced	Linked
Stanford	Score	Yes	Yes	Yes
ANRS	Rules	Yes	Yes	Yes
Rega	Rules	Yes	Partial	Yes
www.hiv-grade.de	Rules	Yes	Partial	Yes
TRUEGENE	Rules	Yes	Yes	No
vircoTYPE HIV-1	Pheno	Yes	N/A	No
GeneSeq HIV Monogram	Rules	Yes	Partial	No

* *Demonstrative sample*

Genotypic interpretation systems*

System	Validation
Stanford	Applied to clinical datasets, comparison to other algorithms. Multiple publications
Rega	"evaluation" on clinical data is done by an independent researcher. database of 23000 sequences with treatment information. These results are then published. Previous algorithms have been evaluated and published.
www.hiv-grade.de	Performance of HIV-GRADE checked in comparison to ANRS and Stanford algorithms on a clinical dataset. Analyses also sent to a panel of selected clinicians to discuss the results and to check general acceptance.
vircoTYPE HIV-1	Association of cPSS calculated using vPT-LM FC predictions and clinical cutoffs with virologic response to combination regimens has been evaluated on unseen validation data
GeneSeq HIV Monogram	Testing the algorithm on data not part of the training data set, at a minimum; optimally by independent correlation to clinical outcome data

* *Demonstrative sample*

Discussion Points

- Pooling our resources and efforts
- How should we be comparing algorithms
- Are current algorithms validated
- Approaches to validation of algorithms
- What needs to be done to achieve proper validation

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- Brendan Larder