Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates with INSTI-Resistance

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Abstract O-01

Introduction

- There remains a need for a new integrase strand transfer inhibitor (INSTI)
  - Once daily, even in patients with INSTI resistance
  - No pharmacokinetic boosting, further improved tolerability, fewer PK/drug-drug interactions, smaller pill size

- Bictegravir (BIC; GS-9883) is a novel, potent once-daily unboosted INSTI
  - in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) as a single tablet regimen for the treatment of HIV-1 infection

Objective

- To phenotypically profile the activity of BIC compared to DTG, EVG, and RAL against patient isolates with INSTI resistance associated mutations

Methods

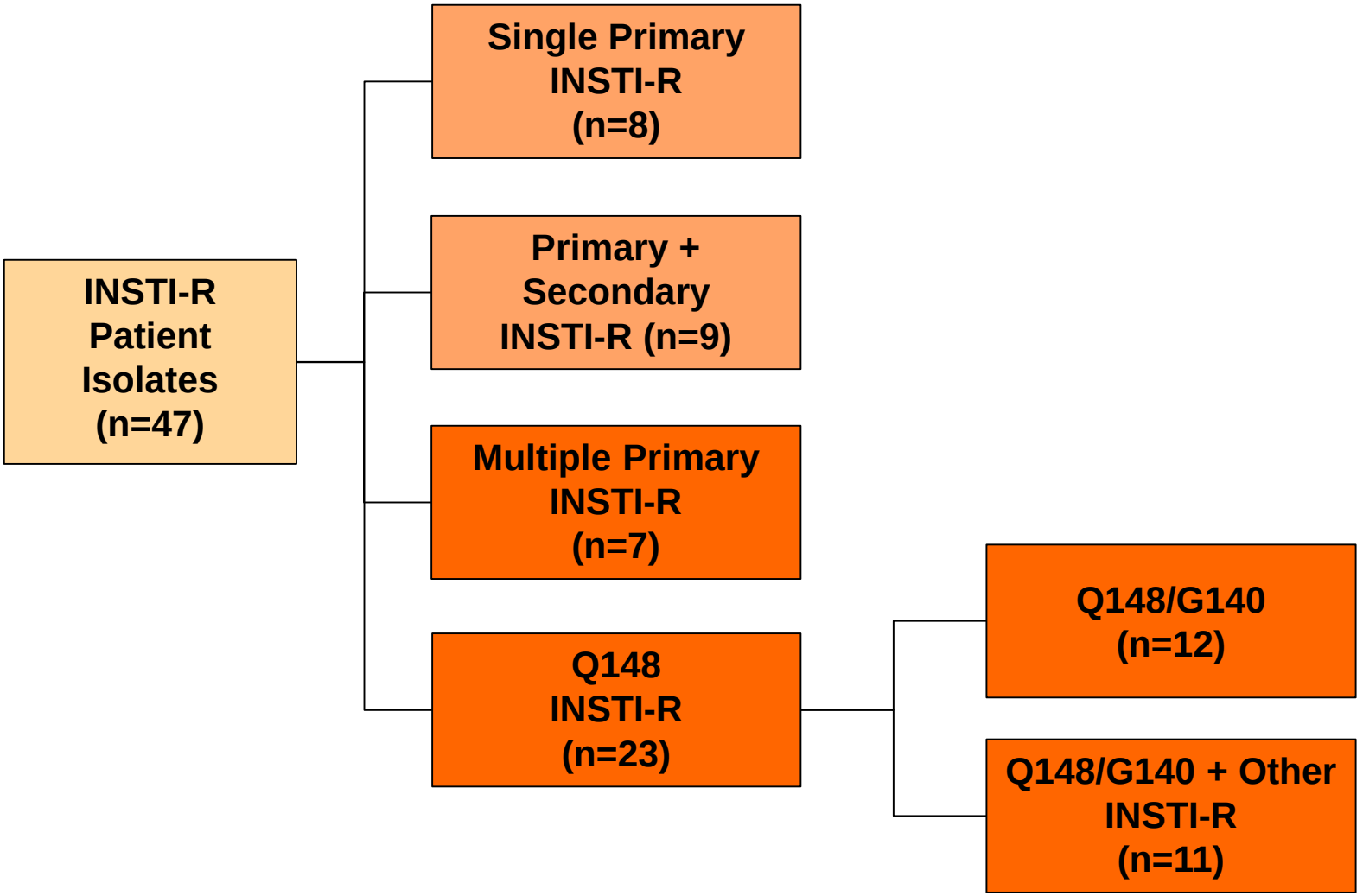
- 47 patient-derived HIV-1 isolates with high-level INSTI resistance were selected from the Monogram Biosciences Phenotyping Panel.
  - All available isolates with >2.5-fold reduced susceptibility to DTG (n=24)
  - as well as a representative panel of isolates with EVG and/or RAL resistance mutations (n=23).
- Phenotype by PhenoSenseIN assay for BIC, DTG, EVG, and RAL

BIC has Potent Activity against Wild-type NL4-3 HIV-1

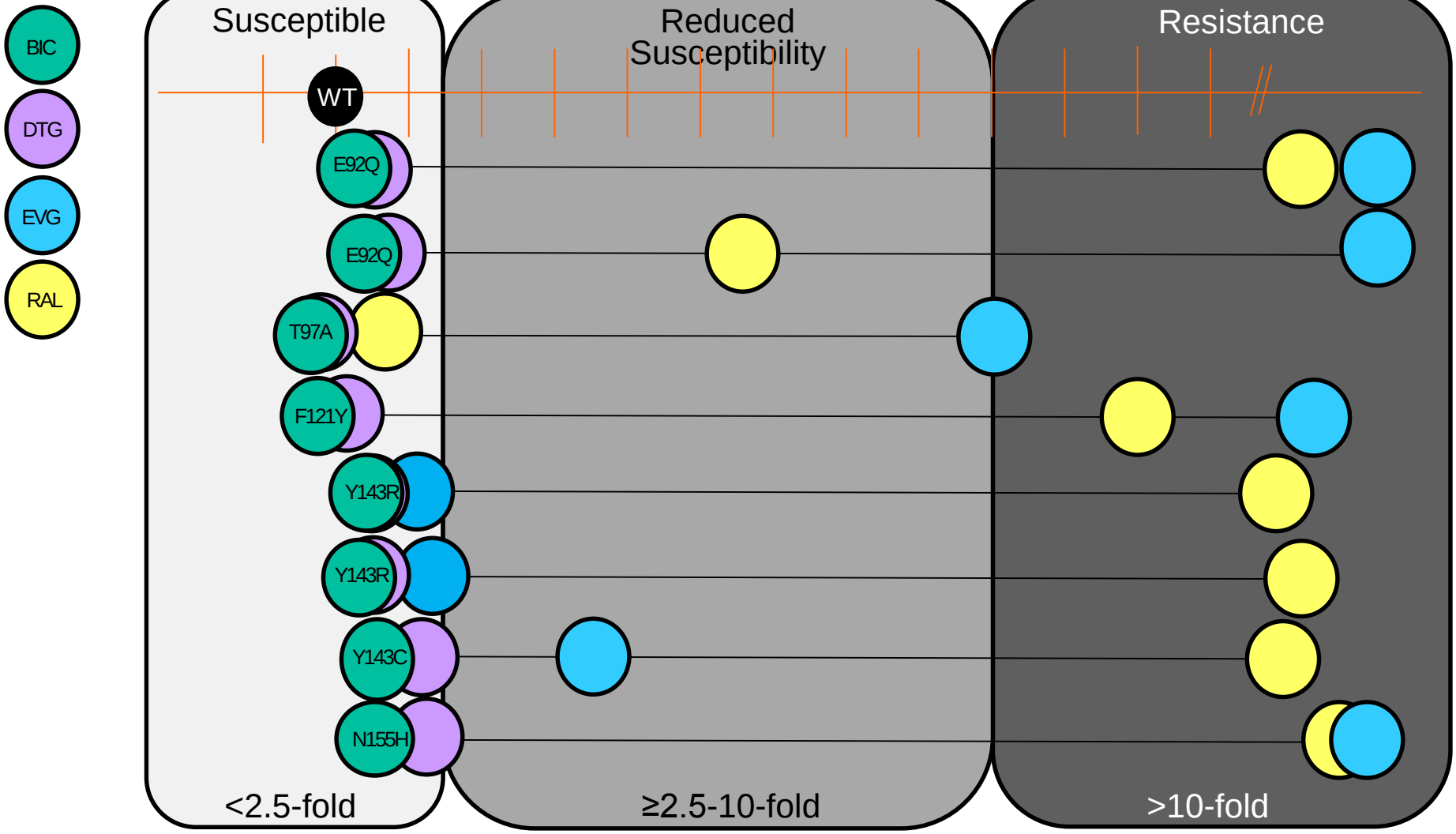
INSTI	Susceptibility (EC_{50} [nM])[a]
BIC	1.9
DTG	2.8
EVG	2.3
RAL	7.1

a. Phenotype of INSTIs against the wild-type control NL4-3 in the PhenoSenseIN assay (Monogram Biosciences)

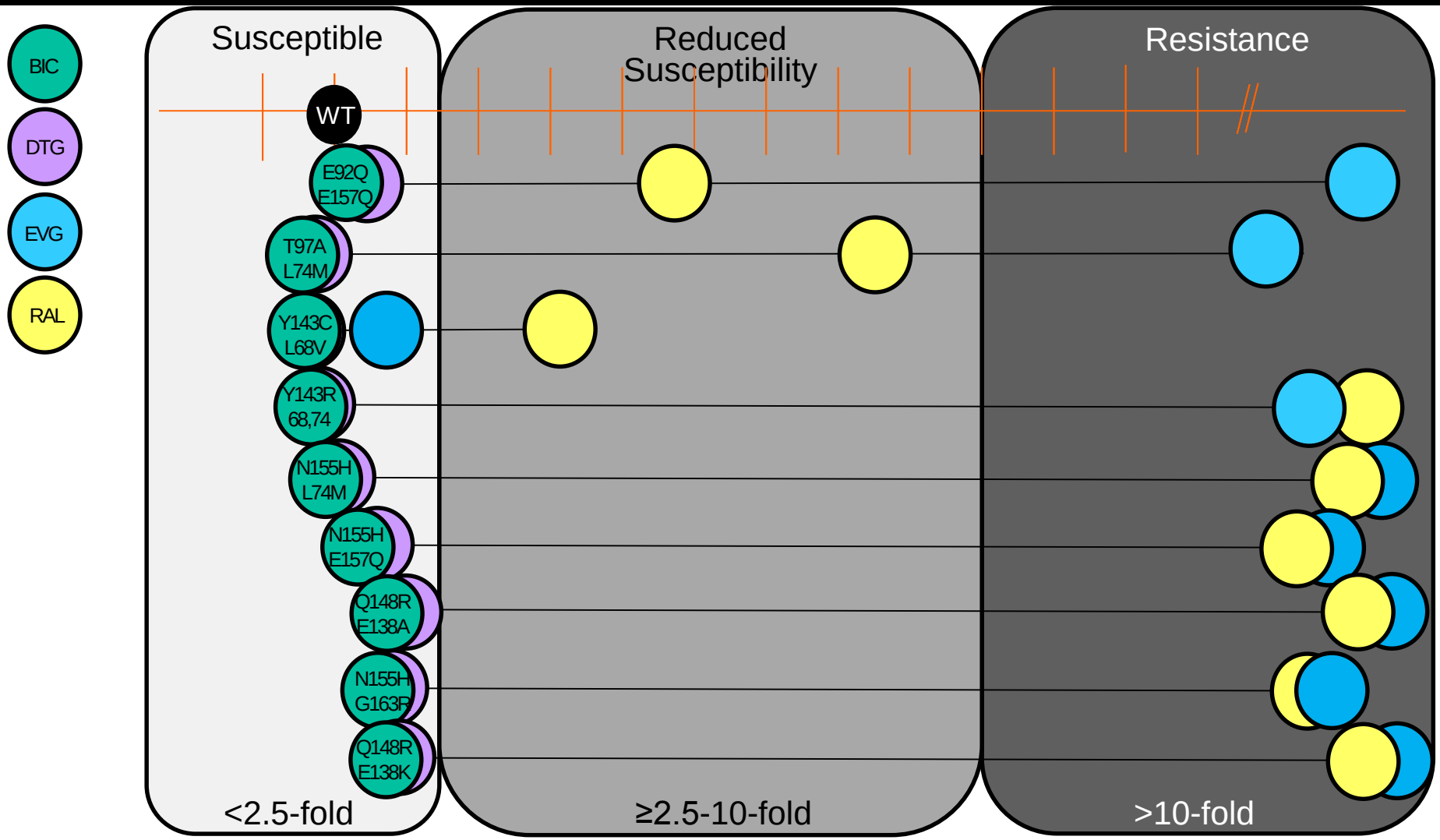
Patterns of INSTI-Resistant HIV-1



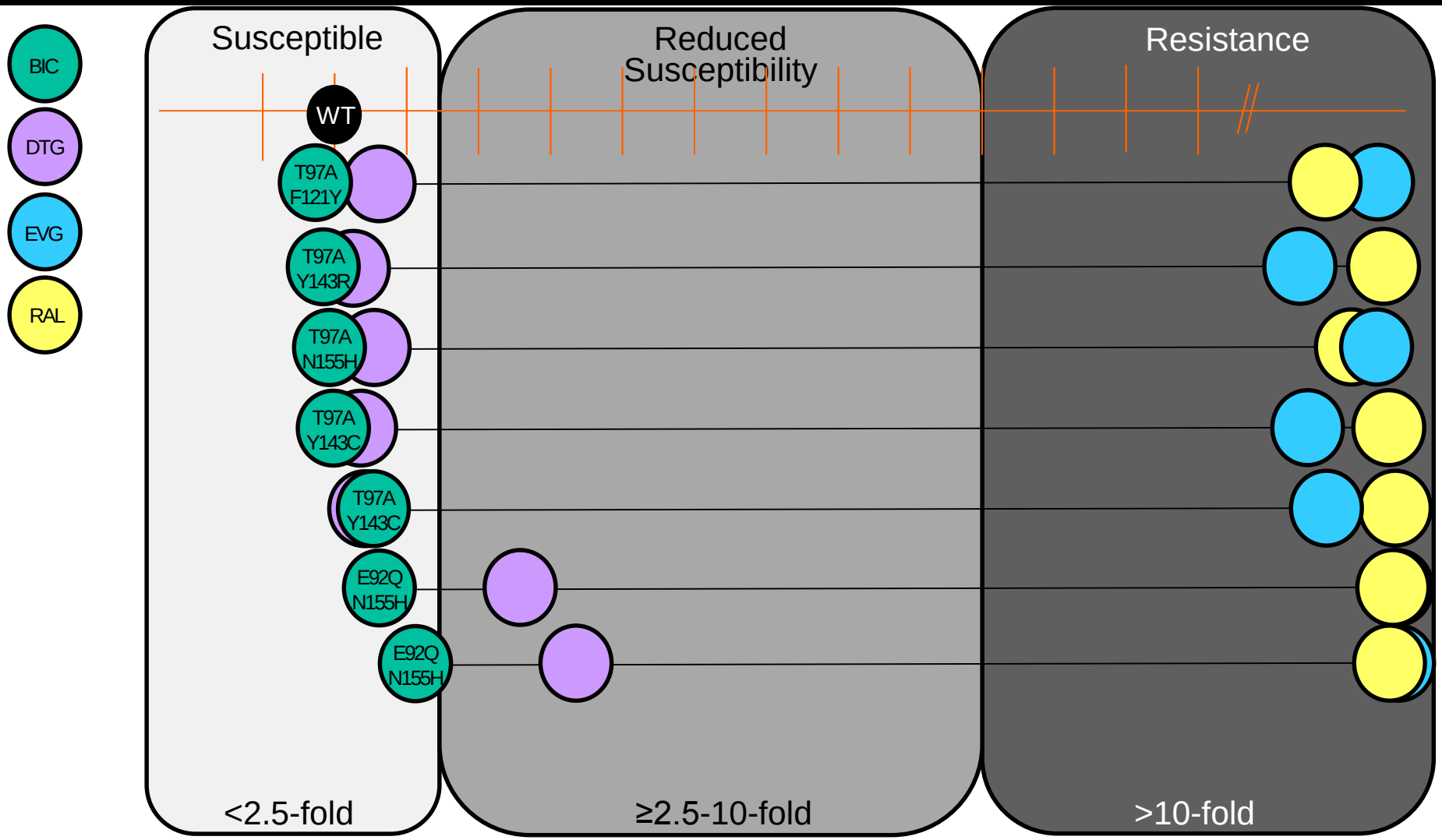
Susceptibility to INSTIs
Single Mutants (n=8)



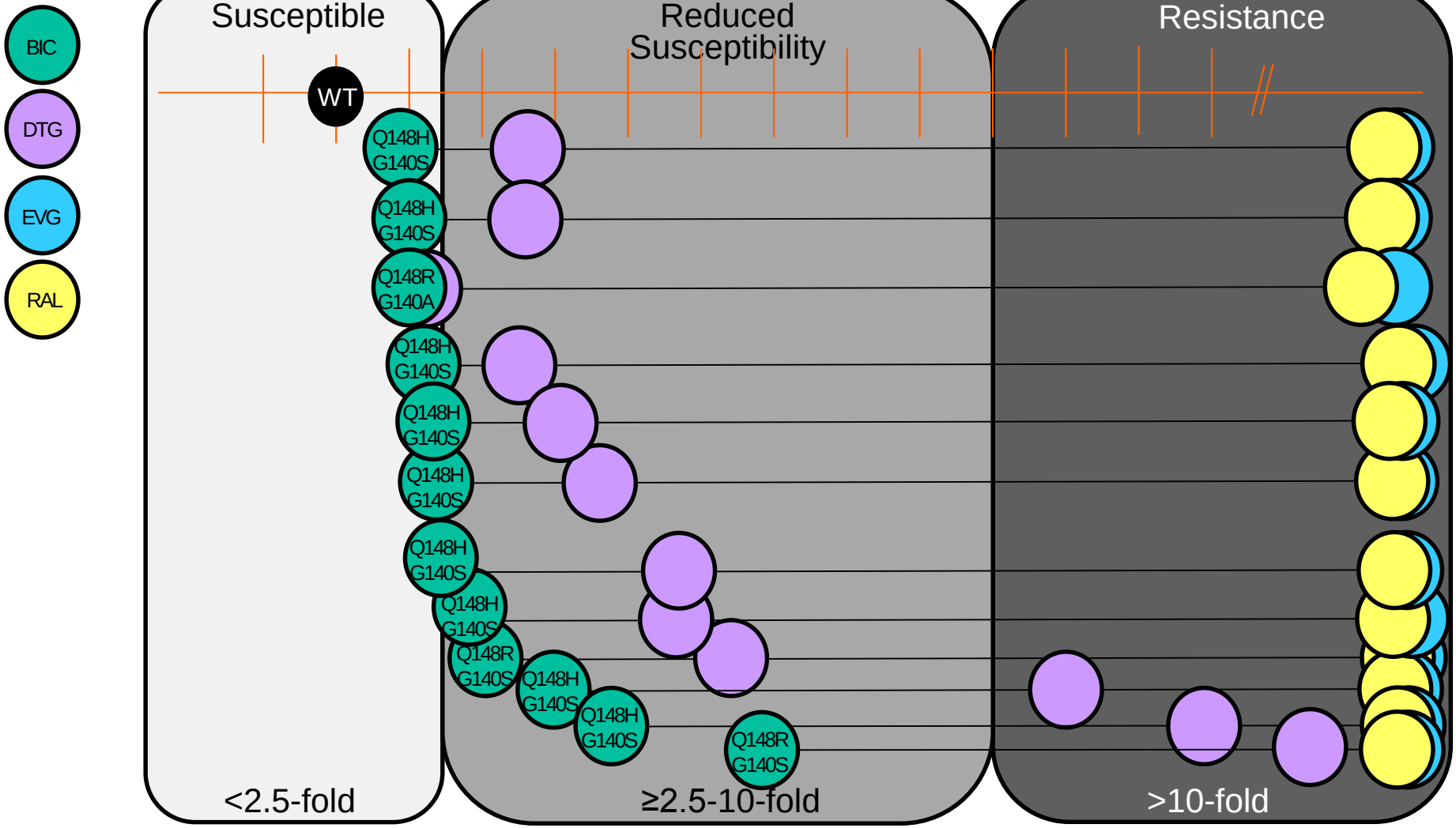
Susceptibility to INSTIs
Primary + Secondary Mutants (n=9)



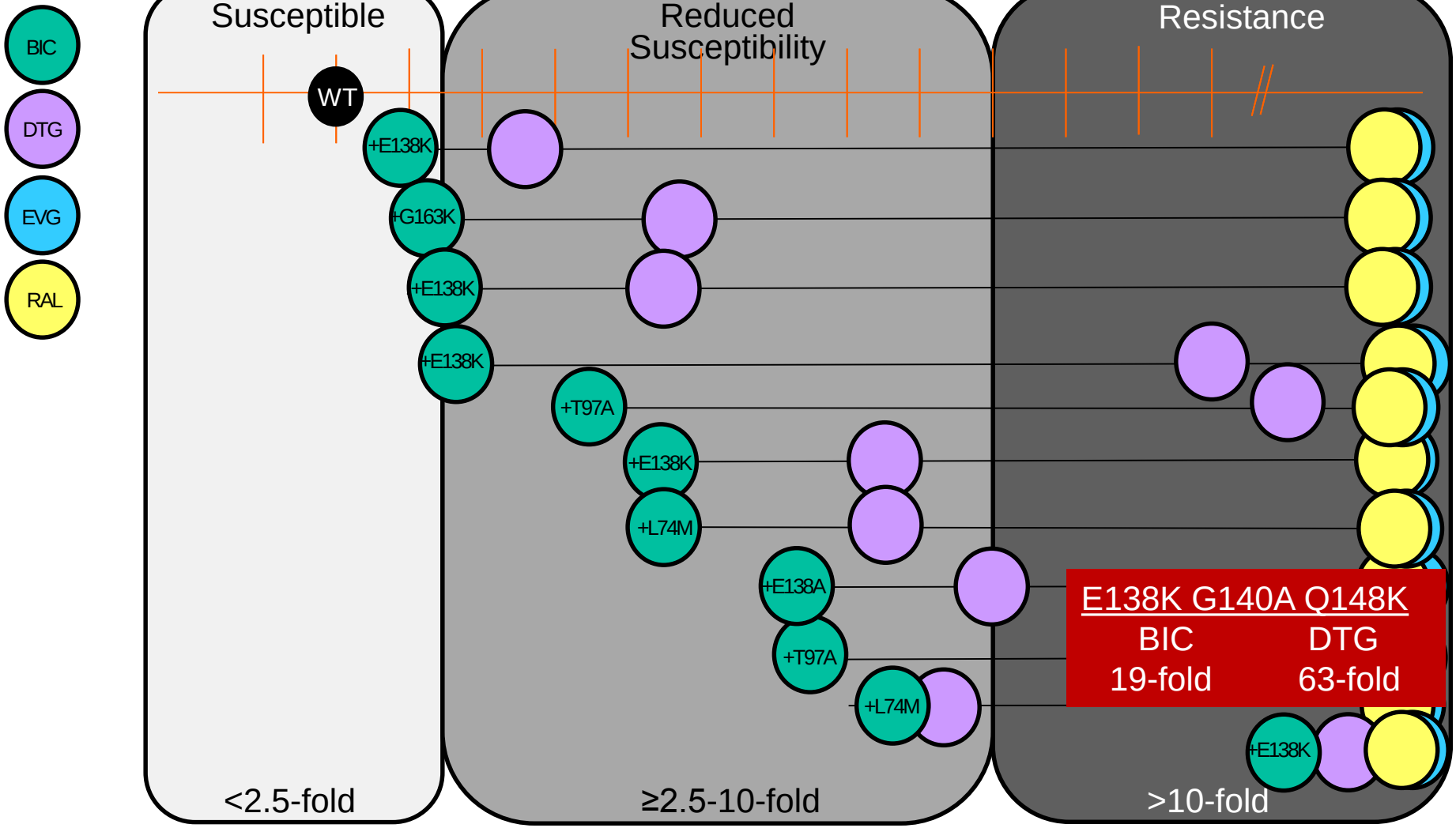
Susceptibility to INSTIs
Muliple Primary Mutants (n=7)



Susceptibility to INSTIs
Q148H/R + G140A/S (n=12)



Susceptibility to INSTIs
Q148H/R + G140A/C/S + Other (n=11)



BIC has Potent Activity Against INSTI-Resistant HIV-1 (n=47)

INSTI	% of isolates (Fold-Change vs. WT)[a]		
	≤2.5	>2.5-≤10	>10-fold
BIC	70%	28%	2%
DTG	49%	34%	17%
EVG	6%	2%	92%
RAL	2%	8%	89%

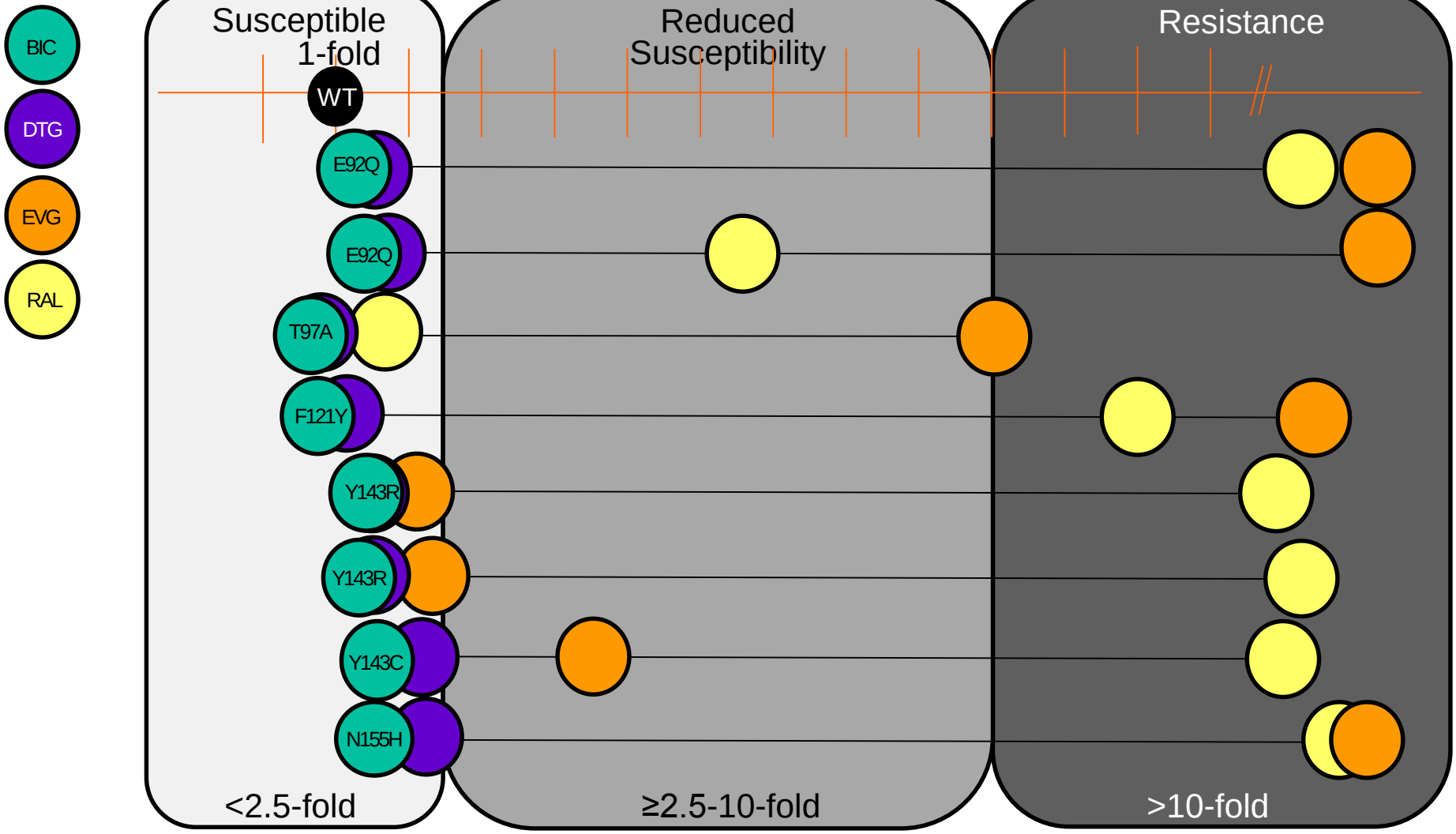
a. Phenotype of INSTIs against 47 patient-derived isolates with INSTI resistance in the PhenoSenseIN assay (Monogram Biosciences)

Conclusions

- Bictegravir (BIC; GS-9883) is a novel INSTI with low nM potency against wild-type HIV-1
- BIC displays an improved resistance profile relative to EVG, RAL, and DTG in patient isolates with high-level INSTI resistance
  - particularly for E92Q+N155H or Q148R/H/K+G140A/C/S in IN
- BIC in combination with FTC and TAF as a single-tablet regimen is in clinical trials for the once-daily treatment of HIV-infected patients

Alternative colors

Susceptibility to INSTIs
Single Mutants (n=8)



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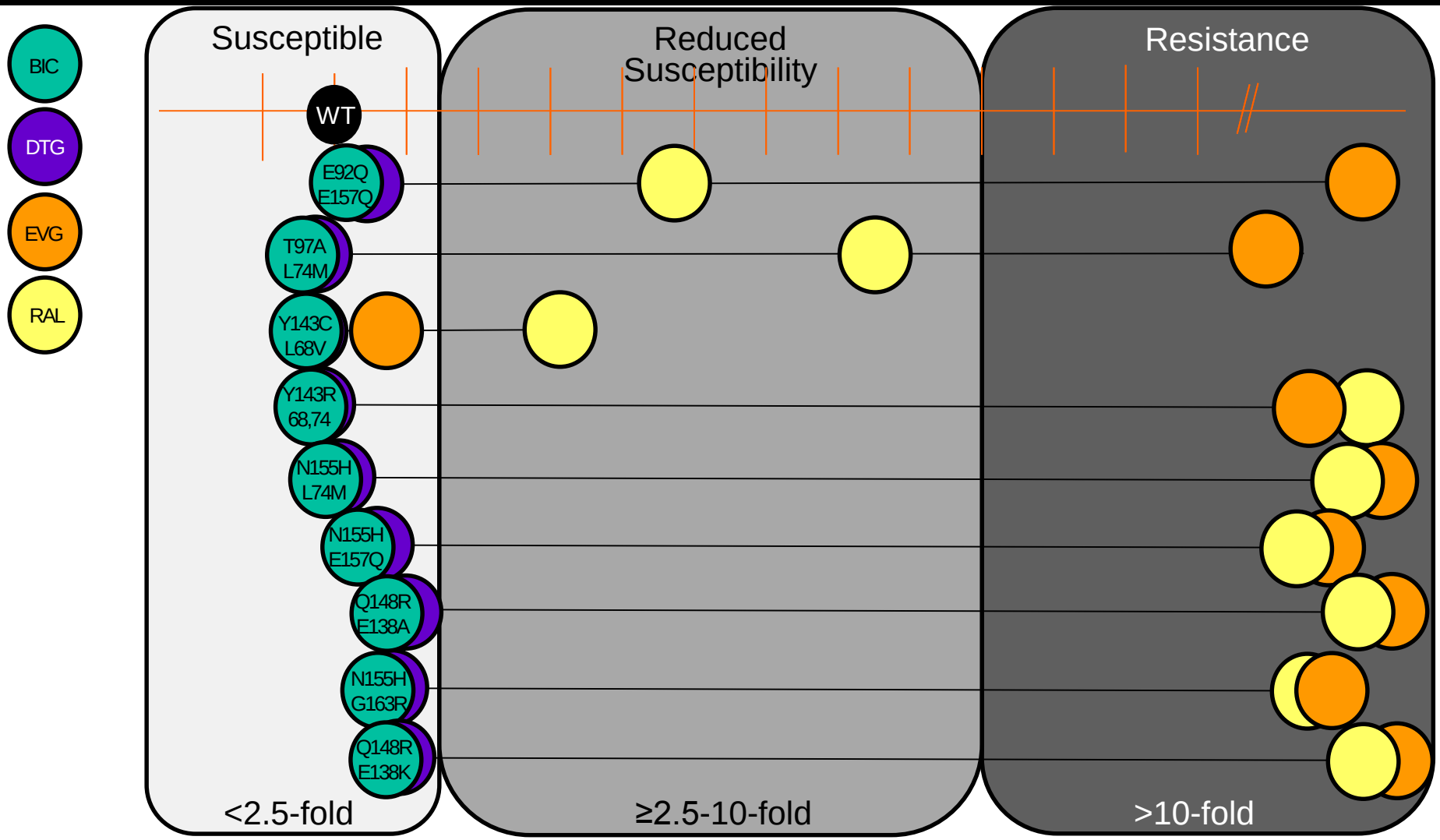
Primary + Secondary Mutants (n=9)



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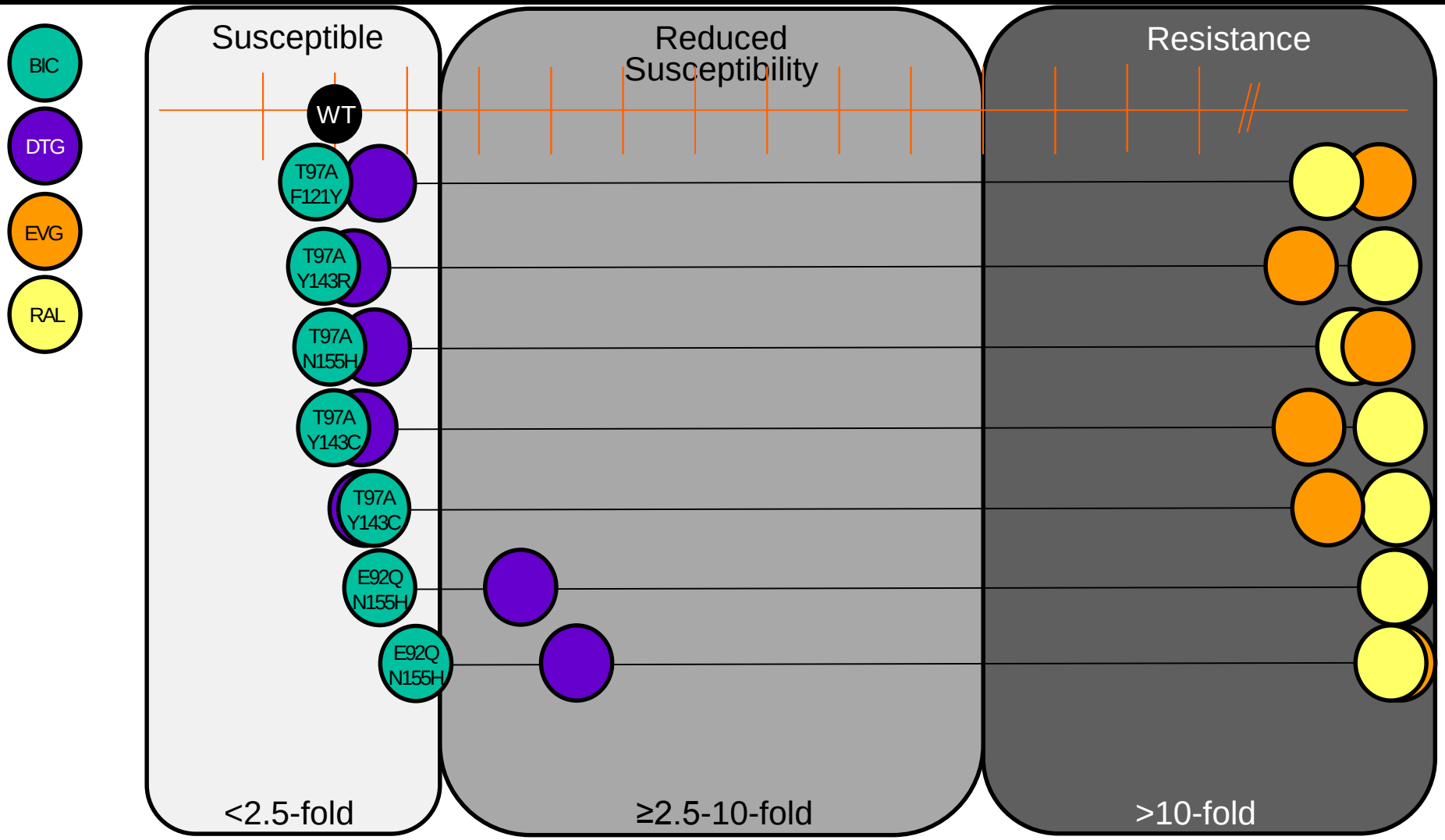

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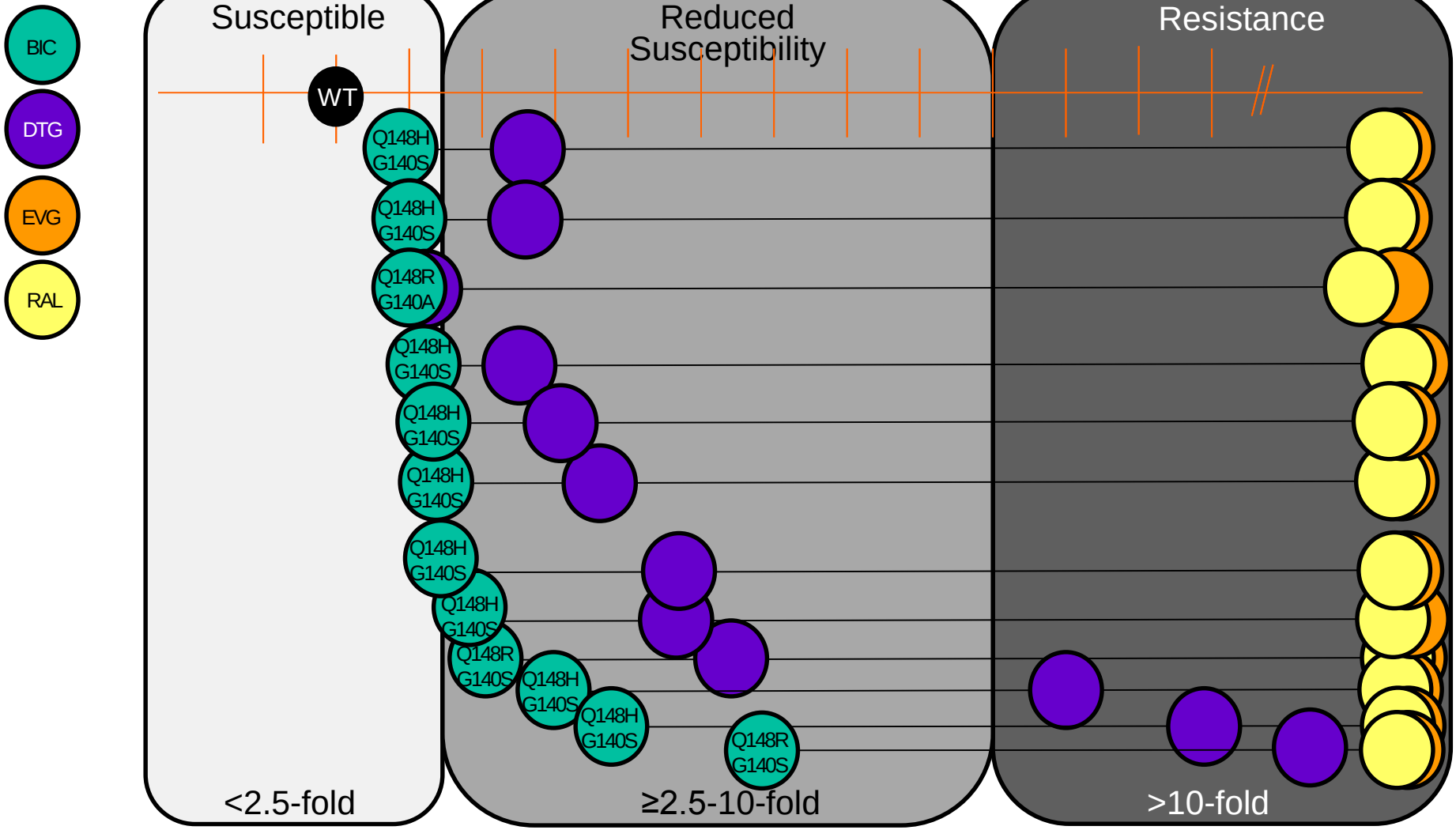
Q148H/R + G140A/S (n=12)



Susceptibility to INSTIs
Q148H/R + G140A/C/S + Other (n=11)