An Informal Survey

Will you consider testing for NS5A resistance before initiating treatment in HCV infected patients?

If yes, why
If no, why

An e-mail was sent to ~100 physicians in Canada
40 physicians responded within 72 hours!

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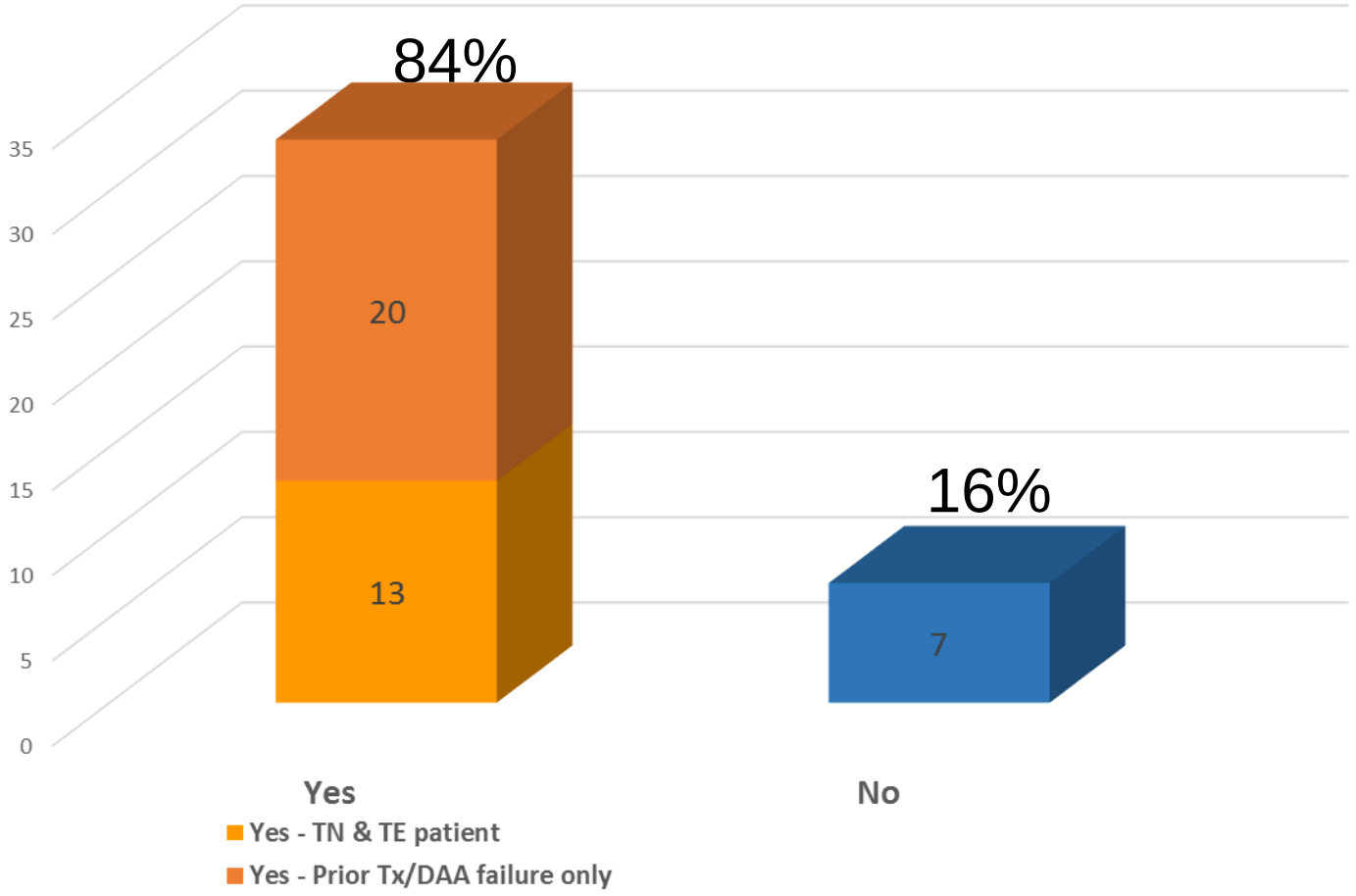


Reasons for NOT SUPPORTING baseline NS5A Resistance Testing

"There is no clinical utility in performing the test with an excellent cure rate"

"the rate of NS5A RAVs with a really significant resistance to DAA is too low ."

"There is currently no non-NS5A inhibitors/interferon-free options approved by Health Canada. I can not decide not to offer a treatment…if I don't have an alternative. "

"what would clinicians do with the information other than worry???

"[It] may even restrict treatment availability without evidence to support this."

"You can treat everyone without knowledge of their RAV status and then deal with the few failures … with salvage regimens"

Reasons for SUPPORTING baseline NS5A Resistance Testing in TN (and TE) PATIENTS

"For an individual patient, you want to know if they have a baseline NS5a conferring high level resistance- this will diminish the likelihood of success to the 50-60% range (ballpark).

"for shortened therapy like 8 wks Harvoni Merck product in gene 1a"

"I would consider for cirrhotic patient"

"A patient who will be unable to response may not have a second chance to be treated due to the very limited budget."

"it would provide more information on the patient's virus and may "fine tune" the choice of medications to achieve the best chance of an SVR"

Reasons for SUPPORTING baseline NS5A Resistance Testing in TN (and TE) PATIENTS

"I would do it to guide treatment and selection of antiviral and decision in adding Ribavirin"

"you might use a NS5a sparing regimen, add RBV and/or treat for a longer duration, or wait to treat with next general NS5a."

"I have been doing baseline resistance to better understand pt population"

"allows to track increasing RAV prevalence in the community over time"

"We do need information regarding the stability of these RAVs and the effect of different agents on these RAVs."

Reasons for SUPPORTING baseline NS5A Resistance Testing in ONLY TREATMENT EXPERIENCED PATIENTS

"In naive, far less predictive and does not impact treatment decisions in current environment."

In failure patients, presence of NS5A resistance mutations predicts high rate of failure

"Definite yes…….because of evidence of their persistence

"Pharmacare has also requested these patients be treated for NS5A resistance before they will consider funding their treatment."

The cost of RAV testing is trivial……compared to the drug cost.

Other noteworthy comments

"You should be asking after AASLD."

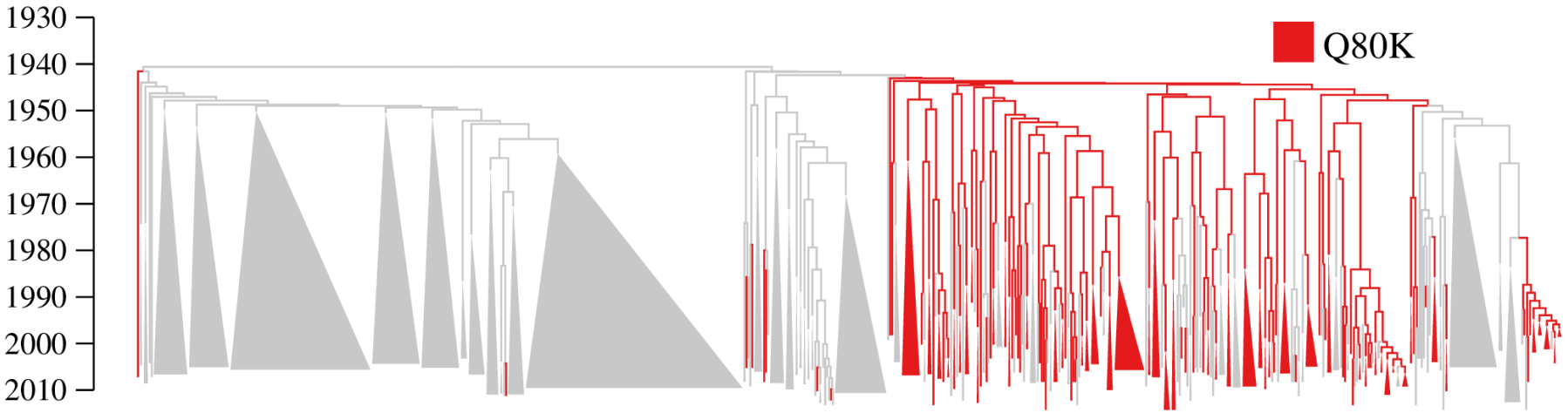
"the most recent data on ASTRAL studies with SOF + Valpatasvir show NO SVR in only 20 / 1035 patients-…"

"If triple therapy shows that BL RAV limitations can be overcome this won't be clinically needed/relevant. "

"Feel money would be better spent on analysing failures and predicting response to retreatment or tailoring retreatment based on RAVS and timing due to reversion to wild type."

"From an infectious disease perspective resistance will become a bigger issue as we have more treatment failures for all sorts of reasons ."

Molecular Tracking of Q80K



96% of GT1a infections carrying Q80K are descended from a single ancestor in which this substitution occurred around 1940

Call for Collaborative Efforts to Understand Baseline NS5A RAVs

1. What is the meaningful variant threshold that can should be used to correlate SVR?

2. Are there consistent criteria to decide which RAVs to be included in the analyses?
   - Based on replicon EC50 fold-shifts? cut-off?
   - Based on RAV frequency in virologic failures?

3. What is the impact of individual RAVs on SVR

4. Should we only include treatment regimens, durations, subjects as per product label in the RAV analyses?

6. There is limited phenotypic information for GT2/3 variants; even more limited for GT4, 5, and 6

7. Difficult to understand prevalence of baseline RAVs; sequences for GT4, 5, 6 are scarce in public databases