Implications for driving based on the conditional risk of seizures after ischemic stroke.

-- ONLINE SUPPLEMENT --

Supplemental Methods: Description of Cohorts

The fullcohort (n=4,552) consisted of nine international subcohorts participating in a registry assessing post-stroke seizures incepted as part of the SeLECT study. Four out of these subcohorts (Austria, Germany (2), Italy, Switzerland (1)) were part of the original SeLECT study, and five (Colombia, Germany (1), Portugal, Spain, Switzerland (2)) were included additionally.

Austria
In the Austrian cohort, people with late seizures and controls (people without late seizures) were randomly selected from a larger cohort of consecutive people with a primary stroke diagnosis admitted to a tertiary referral center in Linz between Jan 1, 2005, and Dec 31, 2014.The study excluded people with transient ischemic attack (n=11), pre-existing brain lesions (i.e., intracranial tumor, trauma, or other; n=7), hemorrhagic stroke (n=97), history of seizures (n=8), cerebral venous thrombosis (n=5), death within days after stroke (n=9), and insufficient follow-up (n=48). Baseline and follow-up data were retrospectively extracted from medical records. 28 (6%) cases received endovascular thrombectomy either with a suction device (until 2011) or using a stent-retriever (from 2011 onwards). All participants included had face-to-face follow-up neurological interviews 3–6 months after stroke and then yearly. Follow-up was terminated after a median of 10 months (IQR 2–41) and whether the participant had late seizures was noted. If seizures were suspected, additional EEG and brain imaging (MRI or CT) were done.

Colombia
The initial Colombian retrospective cohort included patients aged 18 or older with diagnosis of acute ischemic stroke admitted to the stroke unit of a university hospital in Bogota between January 1, 2014, and December 31, 2019 (n=465). Stroke diagnosis was made by a neurologist and confirmed by neuroimaging. Patients with primary hemorrhagic stroke, transient ischemic attack, history of previous seizures and epileptogenic comorbidities (severe traumatic brain injury, brain tumors, history of neurological surgery and sinus vein thrombosis) were not included. Baseline characteristics and follow up information were extracted from medical records. Mean follow-up was 21 months and patients lost to follow-up were excluded (n=116). Additional exclusion criteria were applied for this study, ultimately including a total of 322 patients from the original cohort.

Germany (1)
The German case-control cohort (1) included participants with a first-ever hemispheric stroke admitted to a tertiary referral center in Homburg between January 1, 2010, and December 31, 2016. Screened participants included those that were consecutively evaluated by the Neurology Department. Participants with seizures within the first 7 days after the onset of stroke symptoms were included. Controls were randomly selected among participants with stroke that were admitted during the same time but had no seizures within the first 7 days after stroke. Participants with TIA, primary cerebral hemorrhage or cerebral sinus/venous thrombosis were excluded. Baseline characteristics for cases and controls were independently extracted from medical records by two neurologists and cross-checked for accuracy and completeness. Follow-up was completed at 63 months (IQR 5–68) and data was obtained from retrospective medical chart reviews.

Germany (2)
The German cohort (2) included participants with a first-ever hemispheric stroke admitted to a tertiary referral center in Muenster between Jan 1, 2003, and March 31, 2010. The cohort excluded participants with recurrent stroke (n=225), only infratentorial stroke (n=322), hemorrhagic stroke (n=32), transient ischemic attack (n=64), or cerebral venous thrombosis (n=14). Participants who died in hospital (n=195), died before the interview (n=21), or were lost to follow-up (n=139), and participants declining participation (n=12) were also excluded. Baseline characteristics were extracted from medical records. Follow-up was completed after median 23 months (IQR 12–44) and all participants received a structured telephone interview.

Italy
The Italian cohort was part of a population-based study in the Udine district with 153 312 residents. The cohort included all patients with first-ever strokes occurring between April 1, 2007, and March 31, 2009. The cohort excluded participants with transient ischemic attacks (n=178), previous brain lesions (i.e., brain tumor; the exact number of participants not recorded), non-ischemic stroke (n=156), previous history of seizures or epilepsy (n=22), and missing time-to-event data (n=108), and participants who were deceased or lost to follow-up

(n=94). A neurologist assessed participants within 48 h of admission. All participants were followed up by a face-to-face interview with study neurologists at 1, 6, and 24 months after the stroke.

Portugal
The Portuguese cohort included participants that were part of a prospective longitudinal study of consecutive adults with neuroimaging-confirmed anterior circulation ischemic stroke admitted to the stroke unit of a university hospital in Lisbon over a 24 months period. Those with past medical history of epileptic seizures, traumatic head injury requiring hospital admission, or brain surgery were excluded. All patients received standardized clinical and diagnostic assessment during admission and after discharge. A blinded phone interview and a clinical appointment was conducted at 6- and 12-months after stroke to access the occurrence of epileptic seizures and functional outcome.

Spain
The Spanish cohort included participants that were part of a multicenter prospective longitudinal study evaluating the development of epilepsy in adults aged 18 years or older with acute ischemic or hemorrhagic stroke admitted to one of six hospitals in Catalonia between August 2012 and November 2013. Patients were enrolled at hospital arrival by neurologists. Stroke diagnosis was performed by trained neurologists at each center and confirmed by neuroimaging. The initial study excluded people from whom signed informed consent was not possible to obtain (n=62), had more than 6 hours between symptom onset and emergency room arrival (n=77), tPA was administered previous to blood collection (n=11), was not possible to get blood samples (n=6), had no symptoms at hospital arrival (n=12), no definite diagnosis was made (n=32), or no sufficient blood sample was obtained (n=13). For inclusion in this study, further exclusion criteria was applied: past medical history of epilepsy (n=22), transient ischemic attack (n=101), subarachnoid hemorrhage (n=11), arteriovenous malformation (n=1), subdural hematoma (n=4), and insufficient data from medical reports (n=12). Baseline and follow-up data were collected by chart review and phone interviews. All the patients were clinically monitored during hospitalization, and seizures were clinically diagnosed by certified neurologists.

Switzerland (1)
The Swiss cohort (1) included consecutive people aged 18 years or older with acute first- ever neuroimaging confirmed ischemic stroke admitted to a tertiary referral center in St Gallen, between Jan 1, 2002, and Dec 31, 2008. The cohort excluded people with transient ischemic attacks (n=495), previous history of stroke (n=250), primary hemorrhagic stroke (n=94), previous history of seizures (n=43), re-infarction during follow-up (n=9), and potentially epileptogenic co-morbidities (alcohol or drug abuse [n=60]; intracranial tumors [n=28]; cerebral venous thrombosis [n=11]; history of severe traumatic brain injury [n=12]; history of brain surgery [n=4]; or other, including cerebral arterio-venous malformations, large cerebral aneurysms, cerebral vasculitis, hydrocephalus, and cerebral abnormalities of undetermined etiology [n=15]).85 participants were lost to follow-up or died before follow-up was done. A neurologist analyzed baseline characteristic at admission and a diagnosis of stroke was confirmed at discharge. Brain scan analysis was done using the best available imaging modality (MRI in 954 [80%] of 1200 participants vs CT in 246 [21%]) at discharge. All participants were followed up after a median of 28 months (IQR 21–47) with a structured telephone interview based on a validated questionnaire to detect seizures. In participants who did not have the capacity to do the questionnaire, close relatives, nursing staff, or their general practitioner were interviewed. Positive answers triggered a face-to-face neurological consultation and an electroencephalogram (EEG) to determine the epileptic nature of these episodes and to exclude seizure mimics. If the neurologist suspected a cause of epileptic seizures other than the index ischemic stroke, follow-up imaging was requested to rule out a co-pathology or re-infarction.

Switzerland (2)
The Swiss cohort (2) was part of the Biomarker Signature of Stroke Aetiology (BIOSIGNAL) study, a prospective, observational, multicenter, inception cohort study to evaluate and validate selected blood-biomarkers in patients with confirmed acute ischemic stroke. Participants older than 18 years who were admitted with ischemic stroke and gave informed consent were recruited at the University Hospital Zurich, Switzerland, between October 2014 and April 2022. Participants with transient ischemic attacks were not included. For the pooling of this study patients with potentially epileptogenic co-morbidities including intracranial tumors (n=17), history of severe traumatic brain injury (n=3); history of brain surgery (n=7), or other (cerebral arterio-venous malformations, large cerebral aneurysms, cerebral vasculitis, hydrocephalus, and cerebral abnormalities of undetermined etiology [n=25]) were excluded. There were no participants with a history of seizures before stroke or cerebral venous thrombosis. Three participants were lost to follow-up and 94 died before follow-up was done. The presence of acute symptomatic seizures within the first 7 days after stroke onset was noted in the case report form for each participant. All participants received standardized followed up

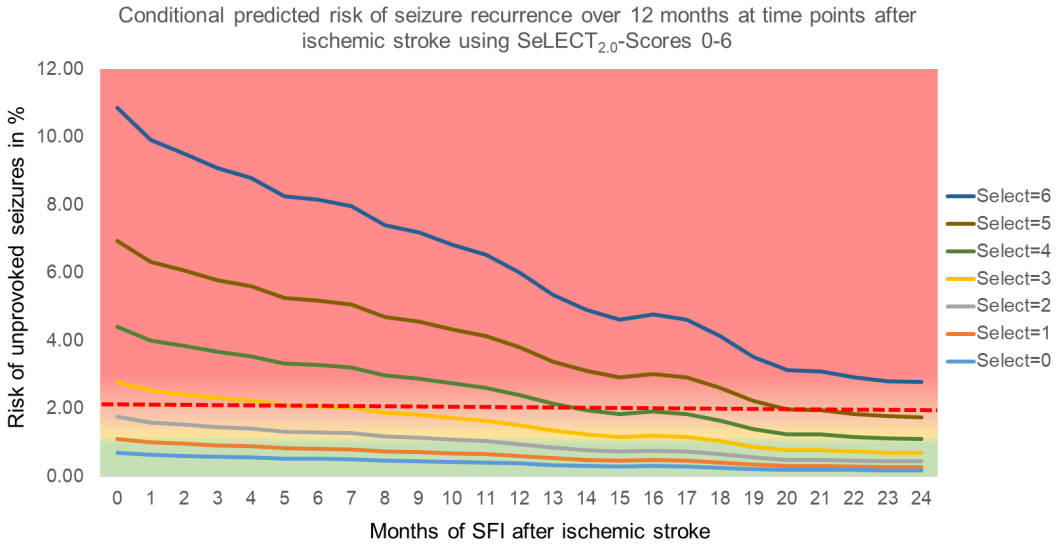
after 3 and 12 months during an outpatient visit or via a structured telephone interview by a neurologist and it was noted whether they had any unprovoked remote symptomatic seizures.

Supplemental Methods: Informed consent procedures

All subjects in the Italian, Spanish, Swiss (2) and Portuguese cohort and those having a face-to-face interview in the Swiss (1) cohort gave written informed consent. All subjects evaluated by telephone in the Swiss (1) and German (2) cohorts gave verbal informed consent. According to Swiss and German law the regional ethical committees exempted these cohorts from requiring written informed consent. The Austrian and German (1) case-control studies were classified as retrospective service evaluation by the regional ethical committee and informed consent was not required. The retrospective Colombian cohort did not require informed consent by the regional ethical committee.

Supplemental Figure 1: Professional Driving: Impact of different SeLECT$_{2.0}$ score values and seizure-free intervals on the chance of an occurrence of a seizure in the next year: **Panel A** displays the impact of different seizure-free intervals (SFI) on the chance of an occurrence of a seizure in the next year (COSY) following ischemic stroke. The lines represent different SeLECT$_{2.0}$scores. Panel B shows the numerical estimates of COSY stratified by different SFIs and SeLECT$_{2.0}$ values including the 95% confidence intervals (values <5% with one decimal place). Colors suggested by different approaches by Bonnett et al. and Marson[1,2](acceptable range of risk for professional driving for COSY < 2% suggested by Schmedding)[3]: risk estimates ≥ 2% (and lower CI ≥ 2%) in redred (="permissive approach");risk estimates < 2% (and higher CI < 2%) in green (="conservative approach"), in orange and yellow: orange when risk estimate ≥ 2% but lower CI< 2% (= "liberal approach"); yellow when risk estimate < 2% but upper CI > 2% (= "intermediateapproach").

A



B

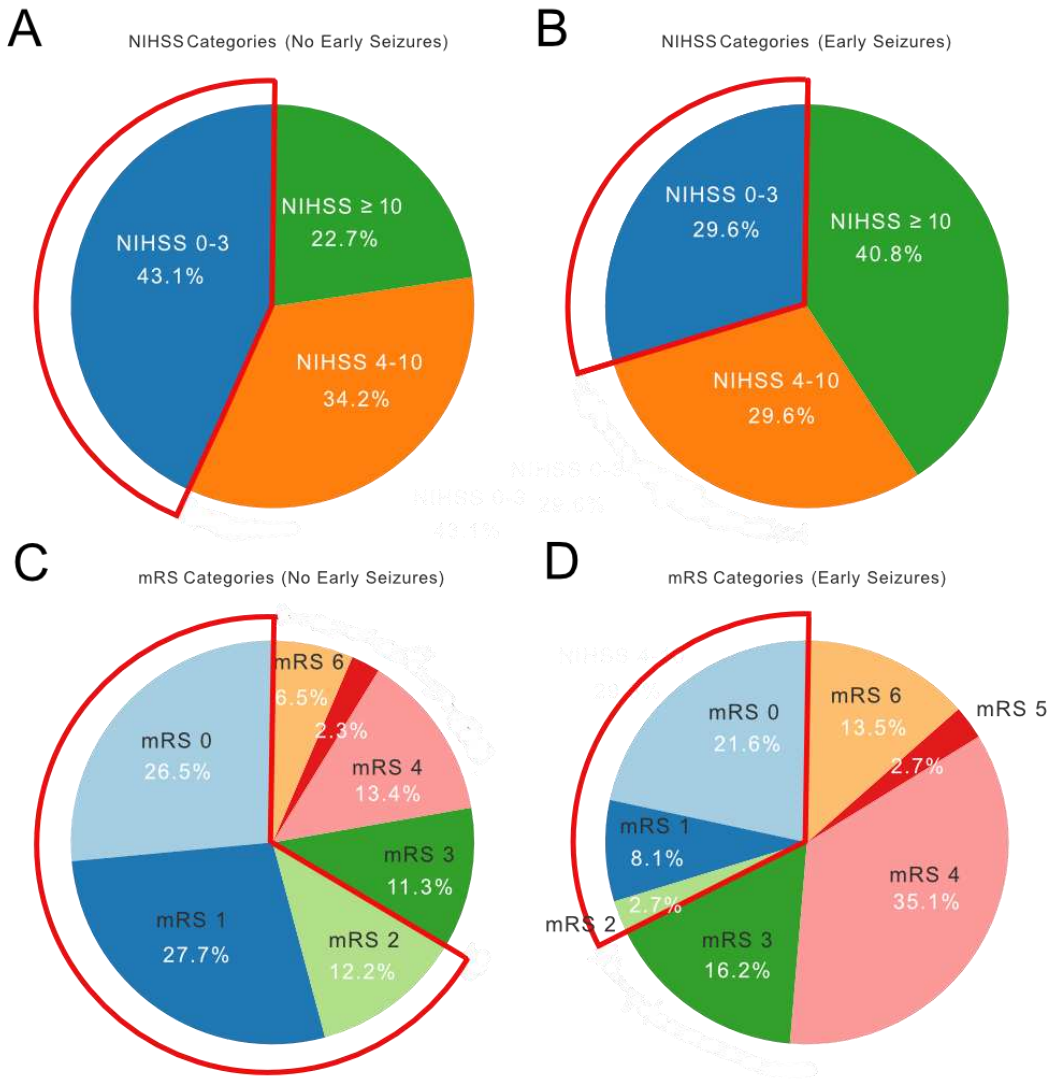
SeLECT 2.0	Risk of unprovoked seizures in % for time points after SFI after ischemic stroke (95% CI) in months								
	0	1	2	3	6	9	12	18	24
6	11 (9-14)	10 (9-12)	10 (8-11)	9 (8-11)	8 (7-10)	7 (6-8)	6 (5-7)	4.1 (3.6-4.7)	2.8 (2.4-3.3)
5	7 (6-9)	6 (6-7)	6 (5-7)	6 (5-7)	5 (4.7-6)	4.6 (4.1-5)	3.8 (3.4-4.4)	2.6 (2.3-2.9)	1.7 (1.5-2.1)
4	4.4 (3.7-6)	4.0 (3.5-4.7)	3.8 (3.4-4.4)	3.7 (3.3-4.2)	3.3 (2.9-3.9)	2.9 (2.6-3.3)	2.4 (2.2-2.8)	1.6 (1.5-1.8)	1.1 (1.0-1.3)
3	2.8 (2.3-3.6)	2.5 (2.2-3.0)	2.4 (2.1-2.8)	2.3 (2.0-2.7)	2.1 (1.8-2.5)	1.8 (1.6-2.1)	1.5 (1.3-1.8)	1.0 (0.9-1.2)	0.7 (0.6-0.8)
2	1.7 (1.4-2.3)	1.6 (1.3-2.0)	1.5 (1.3-1.8)	1.4 (1.2-1.8)	1.3 (1.1-1.6)	1.1 (1.0-1.4)	0.9 (0.8-1.2)	0.6 (0.5-0.7)	0.4 (0.4-0.5)
1	1.1 (0.8-1.5)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	0.9 (0.7-1.1)	0.8 (0.6-1.1)	0.7 (0.6-0.9)	0.6 (0.5-0.7)	0.4 (0.3-0.5)	0.3 (0.2-0.3)
0	0.7 (0.5-1.0)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.7)	0.5 (0.4-0.7)	0.4 (0.3-0.6)	0.4 (0.3-0.5)	0.3 (0.2-0.3)	0.2 (0.1-0.2)

Supplemental Figure 2:Distribution of mRS scores for relevant SeLECT$_{2.0}$scores for private and professional driving

Many patients with severe strokes are not functionally independent (modified Rankin Scale (NIHSS≥4, mRS≥3)[4,5] and will most likely not consider to drive following stroke. In contrast, those who are functionally independent(NIHSS≤3, mRS≤2) after stroke may consider driving. In these cases, estimating COSY with SeLECT$_{2.0}$may be helpful to guide driving regulations, especially in patients with early seizures.

In this regard, we estimated the proportion of functionally independent (NIHSS≤3, mRS≤2) stroke survivors without(maximum SeLECT$_{2.0}$score 6, left**Panels A and C**) or with early seizures(SeLECT$_{2.0}$scores 3-13 possible, right **Panels B and D**). Therefore, weanalyzed NIHSS at admission in all patients (upper **Panels A and B**) and the mRSthree months after the incident event for 997 patients from the Switzerland (2) cohort (lower **Panels C and D**) and calculated the distribution in participants without and with early seizures. We highlighted the proportion of patients with low NIHSS ormRS≤2 (shown as red encircled areas) who potentially are able to drive after ischemic stroke.

To conclude, a substantial proportion of patients in our cohort were functionally independent and may consider to drive after stroke. In these cases, the calculation of the risk of seizures, in addition to considering their stroke-related deficits, may be important to determine their ability to drive.



Supplemental Table 1:*Cross-Validation using a leave-one-cohort-out strategy and calculating Coefficient of variancebetween centers:*

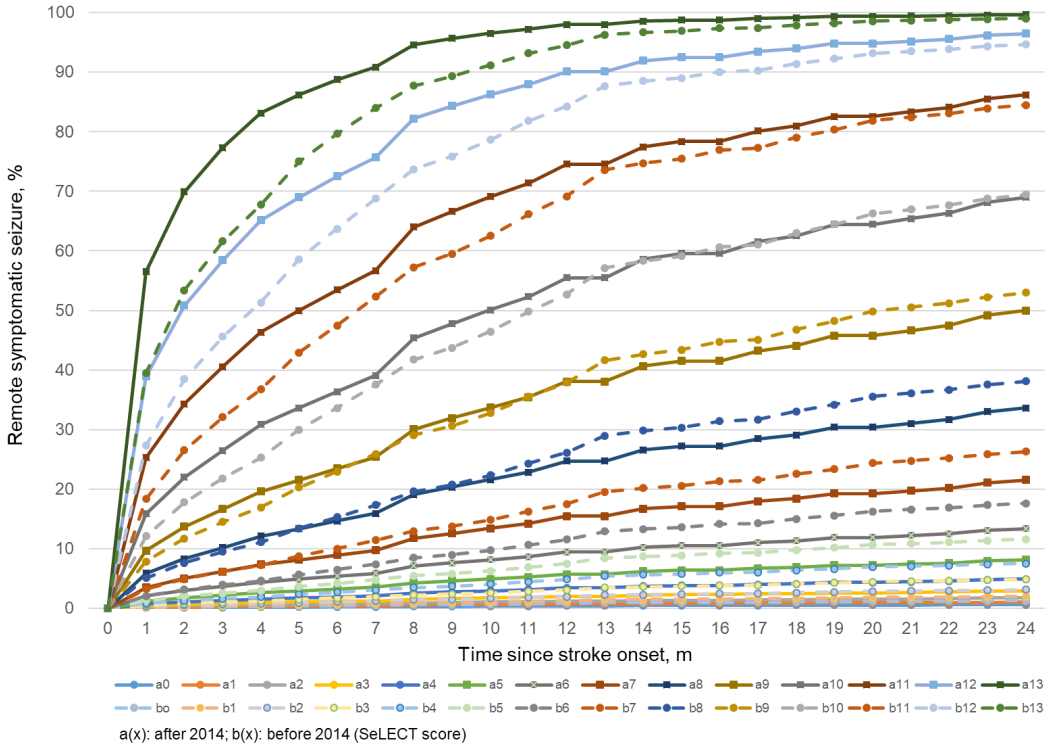
Select-Score$_{2.0}$	CoV 3 month	CoV 12 month
0	0.10	0.07
1	0.09	0.07
2	0.09	0.07
3	0.09	0.06
4	0.08	0.06
5	0.08	0.06
6	0.08	0.07
7	0.08	0.07
8	0.09	0.07
9	0.09	0.07
10	0.09	0.07
11	0.09	0.06
12	0.09	0.04
13	0.09	0.03
mean	**0.09**	**0.06**
min	**0.08**	**0.03**
max	**0.10**	**0.07**

Coefficient of variance (CoV)was used as a statistical measure to determine the relative variability of the subcohorts. We used a leave-one-cohort-out cross-validation. To calculate the CoV, first we divided the subcohorts into nine datasets. For each dataset, we removed one subcohort and calculated the predicted risk of unprovoked seizures at month 3 and 12 for the remaining eight subcohorts. We repeated the mentioned steps for each of the nine subcohorts, so that each subcohortwas left out once. Then we calculated the standard deviations to the means of the nine predictedrisks to obtain the overall CoV(CoV = (standard deviation / mean)). We determined the CoV at months 3 and 12for every SeLECT$_{2.0}$score from 0-13.From this we derived the mean, minimum and maximum value of the CoV at month 3 and 12.In general, a CoV below 15% is considered acceptable and indicates consistency between the different subcohorts/ datasets.

To conclude, all CoV values in our dataset were ≤ 10%, indicating consistency of data.

Supplemental Table 2: *Between-Group Variance (BGV) of groups with data acquired before (n=3214) or after 2014 (n=1338)*

Select-Score$_{2.0}$	BGV 3 month	BGV 12 month
0	<0.001	0.01
1	<0.001	0.02
2	0.001	0.04
3	0.001	0.07
4	0.001	0.12
5	0.001	0.18
6	<0.001	0.23
7	0.01	0.20
8	0.06	0.08
9	0.33	0.19
10	1.37	1.53
11	4.70	4.51
12	13.16	5.82
13	28.38	2.75
mean	**0.004**	**0.19**
min	**< 0.001**	**0.01**
max	**28.38**	**5.82**



BGV (Between-Group Variance) was employed as a metric to assess the disparities between two distinct time periods: data collected prior to 2014 (n=3214) and data collected after 2014 (n=1338). This analysis involved the computation of SeLECT2.0 scores ranging from 0 to 13. For each score, the group means and overall means of predicted values were determined at months 3 and 12. The

differences between each group mean and the overall mean were squared, and these squared differences were then multiplied by the respective group size. The results of these calculations are presented in Supplemental Table 3. They show a small BGV in recent vs. old cohort data.

The accompanying figure illustrates the predicted risk of unprovoked remote symptomatic seizures over a span of 0-24 months following a stroke, corresponding to SeLECT2.0 scores ranging from 0 to 13. The figure showcases distinct lines for data collected before 2014 (depicted as dashed lines) and after 2014 (shown as solid lines).

To conclude, the BGV and the visual analysis indicate high agreement between cohorts acquired recently and older cohorts, indicating little impact of recent treatment advances on our estimates and the stability of our estimates over time.

Reference

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