Prognosis of Incidental Brain Metastases in Patients With Advanced Renal Cell Carcinoma

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ABSTRACT

Background: Metastatic renal cell carcinoma (mRCC) management guidelines recommend brain imaging if clinically indicated and the rate of occult central nervous system (CNS) metastasis is not well-defined. Early detection could have major therapeutic implications, because timely interventions may limit morbidity and mortality. **Patients and Methods:** A retrospective review was performed to characterize patients with mRCC incidentally diagnosed with asymptomatic brain metastases during screening for clinical trial participation at Gustave Roussy and Memorial Sloan Kettering Cancer Center. Descriptive statistics and time-to-event methods were used to evaluate the cohort. **Results:** Across 68 clinical trials conducted between 2001 and 2019 with a median 14.1-month follow-up, 72 of 1,689 patients (4.3%) with mRCC harbored occult brain metastases. The International Metastatic RCC Database Consortium (IMDC) risk status was favorable (26%), intermediate (61%), and poor (13%), and 86% of patients had ≥2 extracranial sites of disease, including lung metastases in 92% of patients. CNS involvement was multifocal in 38.5% of patients, and the largest brain metastasis was >1 cm in diameter in 40% of the cohort. Localized brain-directed therapy was pursued in 93% of patients, predominantly radiotherapy. Median overall survival was 10.3 months (range, 7.0–17.9 months), and the 1-year overall survival probability was 48% (95% CI, 37%–62%). IMDC risk and number or size of lesions did not correlate with survival (log-rank, *P*=.3, *P*=.25, and *P*=.067, respectively). **Conclusions:** This large multi-institutional mRCC cohort study identified occult brain metastasis in a notable proportion of patients (4.3%) and highlights that the risk of asymptomatic CNS involvement extends to those with favorable risk features per IMDC risk assessment. These data provide rationale for brain screening in patients with advanced RCC.

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Background

Brain metastases are a critical site of disease progression in patients with metastatic renal cell carcinoma (mRCC). Large institutional and population-based studies estimate the incidence of brain metastasis to be 5% to 20%,[1–6] and variability in incidence rates partly relates to the fact that brain metastases are typically diagnosed when new symptoms prompt evaluation. Without standardized screening measures, these historical rates provide limited guidance to clinicians, because the true incidence may not include patients with asymptomatic disease who do not undergo evaluation. Efforts to comprehensively identify this patient population are needed, given that multidisciplinary clinical management is often prioritized to limit morbidity and mortality associated with local progression.

Per national and international guidelines standardizing mRCC management,[7–10] brain imaging is recommended at the clinician's discretion and hence is often not performed in the absence of symptoms. However, brain imaging is commonly mandated as a part of eligibility assessments for clinical trial entry. Such uniform screening provides a systematic opportunity to investigate the rate of incidental brain metastasis in mRCC and characterize outcomes in this specific patient population.

Patients and Methods

After obtaining Institutional Review Board approval at Gustave Roussy and Memorial Sloan Kettering Cancer Center, a retrospective multicenter chart review was performed at the participating centers. A combined deidentified database was constructed of patients with mRCC who required brain imaging as a part of eligibility screening for participation in institutional clinical trials and were incidentally diagnosed with brain metastases. Clinical trials that did not require brain imaging and patients who were deemed ineligible for trial participation for reasons other than brain metastasis were excluded. Chart review was performed to confirm the absence of neurologic symptoms at the time of the

screening, including numbness, weakness, dizziness, balance problems, headache, or altered mental status. Documented physical examinations were also screened for any physical signs related to these symptoms. Baseline clinical features collected included demographics and International Metastatic RCC Database Consortium (IMDC) risk status at study screening. Brain metastases were characterized by number, size of largest metastasis (per longest axis diameter), and presence or absence of associated vasogenic edema through review of institutional radiology reports. Patients were managed according to best practices at each center, and site-specific therapeutic interventions and outcomes were recorded. Data cutoff was November 1, 2019.

Continuous variables were summarized using median with minimum and maximum, and categorical data were tabulated using frequencies and percentages. Median overall survival (OS) and 95% confidence intervals were estimated using the Kaplan-Meier method. Survival was measured from diagnosis of brain metastasis until death from any cause, and patients were censored at the time of last follow-up if alive or without subsequent follow-up data. Log-rank testing was used to compare survival outcomes by clinical variables. R version 3.6.1 (R Foundation for Statistical Computing) was used for statistical analyses.

Results

Patient Characteristics

From 2001 through 2019, 68 clinical trials conducted at Gustave Roussy and Memorial Sloan Kettering Cancer Center for patients with mRCC included mandatory brain screening by CT/MRI at study entry. Among 1,689 patients screened, 72 (4.3%; 95% CI, 3.3%–5.3%) were found to have incidental brain metastases without documented neurologic symptoms upon dedicated chart review. Of these 72 patients, 54 (75%) were male, and the median age at mRCC diagnosis was 56 years (range, 37–77 years) (Table 1). At the time of trial screening, 16 patients (26%) had IMDC favorable-risk disease, 37 (61%) had intermediate-risk disease, and 8 (13%) had poor-risk disease. Data were incomplete for full IMDC risk calculation in 11 patients. A total of 63 patients (88%) had undergone nephrectomy, and all patients included in this analysis had a clear-cell histologic subtype, with 6 (8%) harboring sarcomatoid dedifferentiation. At the time of initial RCC diagnosis, 43 patients (60%) presented with metastatic disease, and at the time of brain metastasis diagnosis, 62 (86%) had more than one site of extracranial disease on radiographic assessment. The most common extracranial disease site was lung in 66 patients (92% of those with incidental brain metastases), followed by liver and bone (18 patients each [25%]). Brain metastases were diagnosed in 22 of 832 patients (2.6%) screened for first-line studies, and in 50 of 857 patients (5.8%) screened in the treatment-refractory setting.

Table 1. Baseline Patient Characteristics

Characteristic	n (%)
Patients, N	72
Median age at mRCC diagnosis (range), y	56 (37–77)
Median time from mRCC diagnosis to BM diagnosis (range), mo	16.1 (0.2–162)
Available IMDC risk at study screening	
Favorable	16 (26)
Intermediate	37 (61)
Poor	8 (13)
Unknown	11
History of prior nephrectomy	63 (88)
Systemic therapy	
Treatment-naïve	23 (32)
1 prior systemic treatment	31 (43)
≥2 prior systemic treatments	18 (25)
Clear-cell histology	72 (100)
Sarcomatoid features	6 (8)
Tumor grade	
1	1 (2)
2	13 (24)
3	24 (44)
4	17 (31)
Unknown	17
Stage IV at initial diagnosis	43 (60)
Extracranial organ sites of disease at BM diagnosis	
1	10 (14)
2	33 (46)
≥3	29 (40)
Presence of lung metastases	66 (92)
Presence of liver metastases	18 (25)
Presence of bone metastases	18 (25)

Abbreviations: BM, brain metastasis; IMDC, International Metastatic RCC Database Consortium; mRCC, metastatic renal cell carcinoma.

Brain Metastasis Characteristics

All patients were confirmed by chart review to be asymptomatic at study screening. A total of 45 patients (63%) presented with a solitary lesion, 10 (14%) presented with 2 brain metastases, and 17 (24%) presented with ≥3 lesions. Associated edema by radiographic review was found in 57 patients (79%). A total of 67 patients (93%) had imaging evaluable for size measurements per expert radiologist, and 40 (60%) of those patients had ≤1 cm disease in the longest-axis measurement of the

largest lesion. Additional details regarding brain-specific disease are noted in Table 2.

Site-Directed Therapies

Of the available site-directed therapy follow-up data in 63 patients, 52 (83%) were administered corticosteroids. Of the 63 patients, 61 had additional follow-up available and 57 (93%) underwent site-specific therapy, including radiotherapy in 49 patients (86%), surgical resection in 6 (11%), and combination surgery plus radiotherapy in 2 (4%). Median time from detection of brain metastasis to start of site-directed therapy was 30 days (range, 4–262 days; Table 3).

Survival Outcomes in Patients With Incidental Brain Metastasis

A total of 62 patients (86%) had died in this cohort at the time of data cutoff, and the median follow-up for the 10 censored patients was 14.1 months (range, 0–75 months). Median OS was 10.3 months (range, 7.0–17.9 months) and the 1-year OS rate was 48% (95% CI, 37%–62%; Figure 1). When patients were stratified by IMDC risk status, the survival data for favorable-risk, intermediate-risk, or poor-risk disease were not significantly different when compared using log-rank testing (P=.3; Figure 2). Median OS for the favorable-risk, intermediate-risk, and poor-risk groups was 12.7 months (range, 4.8 months–not reached), 12.4 months (range, 7.4–19.7 months), and 4.5 months (range, 3.8 months–not reached), respectively. The 1-year OS probability of favorable-risk, intermediate-risk, and poor-risk disease was 53% (95% CI, 33%–86%), 52% (95% CI, 38%–71%), and 29% (95% CI, 9%–92%), respectively.

OS did not significantly differ between patients with solitary or multifocal disease (log-rank, P=.25), with a 1-year OS probability of 57% (95% CI, 44%–74%) and 33% (95% CI, 19%–58%), respectively (Figure 3A).

Table 2. Brain Metastasis Characteristics

Characteristic	n (%)
Patients, N	72
Solitary lesion	45 (63)
Multifocal	27 (38)
2 lesions	10 (14)
≥3 lesions	17 (24)
Associated edema present	57 (79)
Size of brain metastases (longest axis, largest lesion)	
≤1 cm	40 (56)
>1 cm	27 (38)
Unknown	5
If >1 cm, median size of CNS metastasis (range), cm	1.75 (1.1–5.1)

Abbreviation: CNS, central nervous system.

Table 3. Brain Metastasis Site-Directed Therapy

Brain Metastasis Treatment Summary	n (%)
Patients, N	61
Corticosteroids administered[a]	52 (83)
Site-specific therapy administered	57 (93)
Stereotactic radiotherapy	41 (72)
Whole-brain radiotherapy	8 (14)
Surgical resection	6 (11)
Radiotherapy + surgical resection	2 (4)
Median time between imaging and site-directed therapy[b] (range), d	30 (4–262)

[a]Medically directed treatment data were available for 63 patients.
[b]Radiotherapy or surgery.

Median OS for patients with solitary disease and multifocal disease was 14.2 months (range, 9.5–21.6 months) and 5.8 months (range, 4.1–18 months), respectively. When patients were further stratified by degree of multifocal disease (Figure 3B), those with >2 brain metastases were found to have a 1-year OS probability of 21% (95% CI, 8%–57%) and a median OS of 4.4 months (range, 3.8 months–not reached). The OS comparison between patients with solitary disease and those with ≥2 brain metastases also did not show any significant difference (log-rank, P=.067). When stratified by patients with ≤1 or >1 cm disease, no differences were seen in OS (log-rank, P=.21) (Figure 4). The 1-year OS probability and median OS for patients with ≤1 versus >1 cm disease were 49% (95% CI, 35%–68%) and 12.7 months (range, 7.2–33.5 months) versus 52% (95% CI, 36%–76%) and 10.6 months (range, 5.9–17.9 months), respectively. Survival outcomes integrating size and number are summarized in Figure 5; no formal statistical comparison was performed given the limited subgroup size.

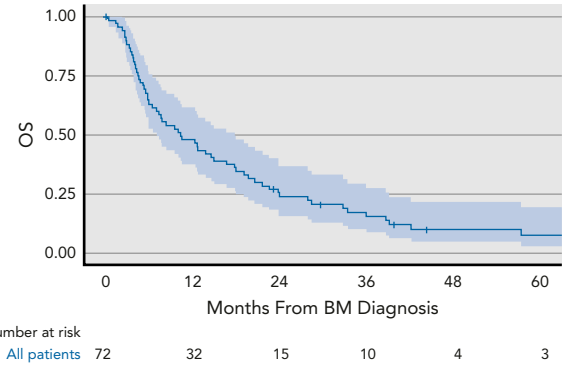

Figure 1. OS from diagnosis of brain metastasis in RCC. OS was assessed using the Kaplan-Meier method, with a median follow-up of 14 months (95% CI, 3.7–75.6).
Abbreviations: BM, brain metastasis; OS, overall survival; RCC renal cell carcinoma.

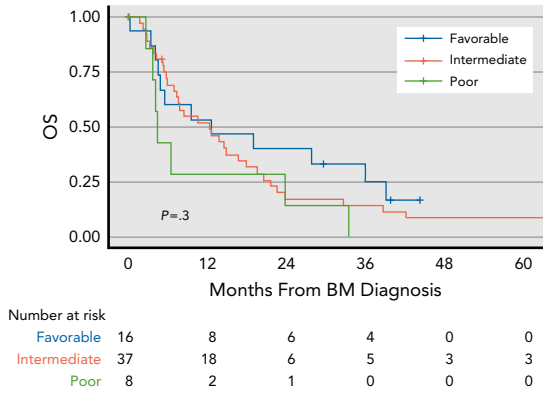

Figure 2. OS by IMDC risk score from diagnosis of brain metastasis. IMDC risk status was assessed at trial screening, and OS was assessed using the Kaplan-Meier method.
Abbreviations: BM, brain metastasis; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; OS, overall survival.

Discussion

This large, multi-institutional retrospective study of patients with mRCC who underwent mandatory brain screening as part of clinical trial entry provided a unique opportunity to systematically assess the rate of incidental brain metastatic disease. Among the 1,689 patients who underwent screening, 72 (4.3%) were found to harbor asymptomatic brain metastases, with a higher incidence among patients previously treated with systemic therapy. This cohort of patients had a median 1-year OS probability of 48% and a median OS of 10.3 months. Application of IMDC risk status and other brain-specific metrics, including metastasis size and number, were not significantly associated with OS outcomes.

These results add to the increasing body of literature evaluating the incidence of brain metastases among patients with mRCC and their outcomes, and add clarity to a commonly overlooked group of patients: those who present incidentally with central nervous system (CNS) disease. Prior reports exploring the SEER program have estimated that 12.1% of patients with mRCC had brain metastasis at diagnosis, with a total of 20.4% in the total mRCC population.[2] Other patient series have identified relative similar incidences,[1,3] with a single institutional dataset highlighting that 32.6% of a total cohort of patients with brain metastasis (7.4% of 1,855 patients with mRCC evaluated) had asymptomatic disease presentation.[3] A more contemporary dataset of patients with mRCC showed an overall frequency of brain metastasis of 28.4%, which may also reflect the adoption of improved imaging techniques for detection, such as MRI, and an increased awareness of the benefit of brain screening.[4] Interestingly, the single institutional dataset showed that IMDC risk status remained prognostic, particularly in the poor-risk disease group, contrary to the current study's finding. This difference may reflect discrepancies in the patient population, given that the dataset presented here consists of asymptomatic patients only and may differ from an all-comer cohort. In addition, our cohort exclusively included patients considered for clinical trial participation, which may introduce a selection bias toward more fit patients. Notably, in KEYNOTE-426, the registration phase III study of pembrolizumab + axitinib, 22 patients (2.1% of the screening population) were not eligible due to active CNS metastases and/or carcinomatous meningitis at trial screening, and this remained the most common reason that patients were unable to participate due to an exclusion criteria.[11] In the phase III METEOR trial of cabozantinib in the second-line setting, 264 of 922 patients (28.6%) were ineligible at screening, and brain metastases requiring treatment were a primary

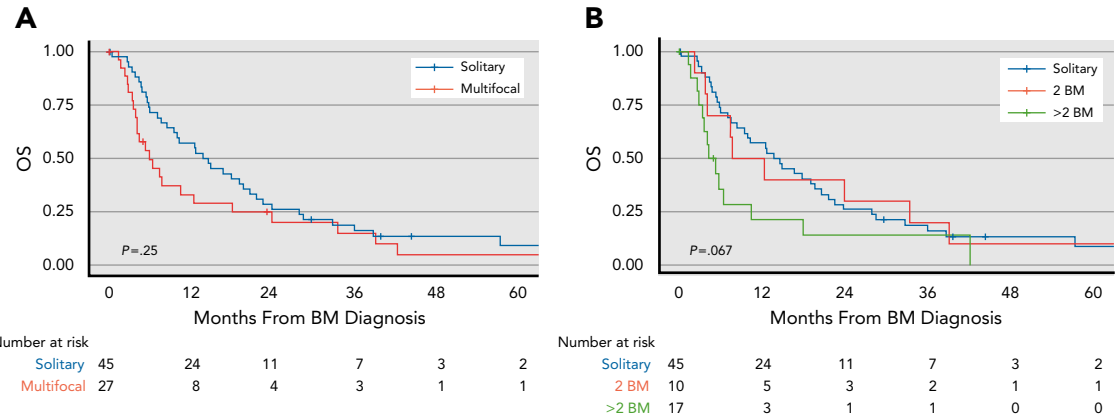

Figure 3. OS by solitary versus multifocal brain metastases. Patients were grouped by either (A) solitary versus multifocal disease or (B) further stratified by the number of specific lesions. Median OS was not significantly different between these groups by log-rank testing (P=.25 and P=.067, respectively).
Abbreviations: BM, brain metastasis; OS, overall survival.

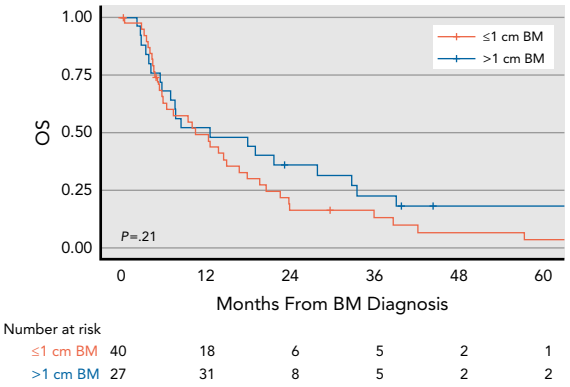

Figure 4. OS by size of largest brain metastasis. Radiographic imaging was reviewed, and the largest isolated brain metastasis in the long axis was used to stratify subcentimeter and >1 cm disease.
Abbreviations: BM, brain metastasis; OS, overall survival.

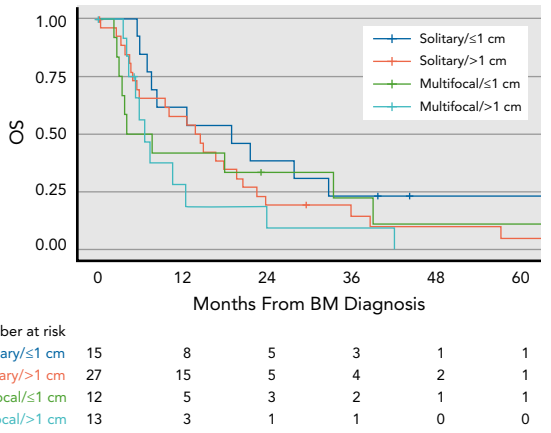

Figure 5. OS by size and focality of brain metastases. The patient cohort was subdivided based on solitary or multiple lesions and ≤1 cm disease. Median OS for the solitary ≤1 cm group and multifocal >1 cm group was 19 months (range, 7.7 months–NR) and 6.5 months (range, 5.3 months–NR), respectively. Formal statistical comparison was not performed.
Abbreviations: BM, brain metastasis; NR, not reached; OS, overall survival.

reason.[12] Although clinical information detailing whether those patients had incidental disease is unavailable for both trials, the rate seen in the first-line setting is consistent with our findings (2.6% in our cohort).

Several factors have been proposed to be associated with the presence of brain-specific metastatic disease, including sarcomatoid dedifferentiation, primary tumor size, regional node involvement, and thoracic and osseous sites of extracranial disease.[6,13] Similar to the latter, we found a notably high proportion of patients with concurrent metastases to the lung (92%). Furthermore, in our cohort, occult CNS disease developed in the background of stage IV disease at initial diagnosis at a remarkably higher rate than in historical controls (60% vs 30%, respectively).[14,15] Although we were unable to compute the incidence per IMDC risk category (IMDC risk scores were unavailable for all 1,689 patients screened), 26% of patients in our cohort had IMDC favorable-risk disease at the time of screening and brain metastasis diagnosis. This finding suggests that screening considerations in routine practice should not be limited to patients deemed to have high-risk disease per standard criteria, and should be considered in patients with high metastatic burden.

In terms of brain-specific characteristics of metastatic disease, lesion size has previously been associated with symptoms,[3,5] whereas lesion number has been associated with lower OS.[16] In our cohort, we compared features of systemic disease and CNS involvement with OS outcomes. Although numerically, brain-specific features including lesion number and size differed in terms of their association with OS, the presence alone of brain metastases seemed to largely impact outcomes in this asymptomatic disease cohort rather than individualized CNS disease metrics. Although no significant differences were identified among IMDC risk groups, the median OS was low even among favorable-risk and intermediate-risk groups. This finding highlights that patients with brain metastasis may have a relatively poor prognosis even when diagnosed in the occult setting, and the presence of metastasis alone for this disease site bears significant weight.

The landscape of therapeutic options for patients with mRCC continues to rapidly evolve, with impressive response rates and superior survival outcomes seen in response to combination immune checkpoint inhibitors[17] and combination vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) plus immune checkpoint inhibitor therapies.[12,18] However, patients with brain metastases are usually excluded from studies, and therefore experience with and activity of these agents in this setting (either asymptomatic or symptomatic) remain limited. Retrospective data suggest that TKI use within 30 days may increase the rate of radiation necrosis[19] or could lead to disease flare.[20] However, anecdotal case reports have also highlighted monotherapy responses using next-generation VEGFR-TKIs such as cabozantinib in radioresistant brain tumors.[21] In a review of prospective studies of patients with brain metastases, sunitinib monotherapy was not shown to have an objective intracranial response.[22] Updated results have been reported from the NIVOREN brain metastasis cohort, a prospective study assessing nivolumab monotherapy in both patients who were treatment-naïve and those treated for brain metastasis.[23] In that cohort of 73 patients, the intracranial response rate was 12% for patients who were treatment-naïve, with no response seen in tumors >1 cm; the median intracranial progression-free survival (PFS) was 2.7 months and the

1-year OS probability was 67%. Notably, all patients enrolled in NIVOREN have at least one lesion >5 mm to assess for response, and it remains to be seen how these agents may impact patients with lower disease burden. Preliminary results evaluating combination ipilimumab and nivolumab (CheckMate 920; ClinicalTrials.gov identifier: NCT02982954) in patients with mRCC and asymptomatic brain metastases are encouraging, with a preliminary reported PFS of 9 months and a systemic objective response rate of 28.6%.[24] Furthermore, preliminary post hoc analyses from JAVELIN Renal 101, the phase III study of axitinib + avelumab versus sunitinib, have shown a similar observed PFS between treatment groups in patients who enrolled with brain metastasis.[25]

Although the evaluation of mandatory trial screening offers a standardized opportunity to limit clinician biases in screening for brain metastases, a major limitation of this dataset remains a selection bias for those patients who considered enrollment in a clinical study and the limited total cohort size for robust comparative analyses. Because this study was performed across several clinical trials, it is important to note that the absence of documented neurologic symptoms is not a substitute for dedicated neurologic evaluation or interview. Furthermore, in addition to other limitations inherent in retrospective analyses, capturing all treatment-related follow-up remains incomplete and comparison between this asymptomatic patient population and those diagnosed with symptomatic disease is challenging. Further work that compares these 2 populations will be integral in reforming clinical decision tools and management guidelines at the population level. For instance, this dataset highlights a higher incidence of brain metastases in previously treated patients, those with metastatic disease at initial presentation, and those with lung involvement. These characteristics may serve as crude metrics to identify high-risk patient populations in whom screening would add value.

In sum, this study highlights that a relevant proportion of patients with mRCC may harbor occult brain metastases, of which most were found at study screening in the treatment-refractory setting. These results provide perspective for treatment guidelines that impact active surveillance or treatment paradigms in patients with advanced disease. Given that this site of diagnosis is often associated with high morbidity, mortality, and urgent multidisciplinary care, these data provide support for broadly applied screening measures, particularly in patients who experience disease progression on first-line therapies, those who initially present with metastatic disease at diagnosis, and those with pulmonary metastases or several sites of extracranial disease. Further efforts that improve on current screening decision trees to identify patients with occult brain disease may allow early intervention and therapeutic action.

Conclusions

This study highlights that 4% to 5% of patients with mRCC may harbor metastatic occult brain disease. Neither incidence nor outcomes were apparently associated with IMDC risk status in this cohort. Screening should be considered for patients with high metastatic burden or those who have experienced disease progression after first-line therapies. Consistent evaluation of risk and identification of algorithmic screening approaches may further characterize high-risk populations.

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