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Use of Patient-Reported Outcomes to Understand & Measure the Patient Experience of Novel Cell and Gene Therapies

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Abstract
Patient reported outcomes (PROs) are the gold standard for assessing patients' experience of treatment in oncology, defined in the 21st Century Cures Act as information about patients' experiences with a disease or condition, including the impact of a disease or condition, or a related therapy or clinical investigation on patients' lives; and patient preferences with respect to treatment of their disease or condition [1]. PROs provide a comprehensive assessment of the benefits and risks of new medical products, as well as essential data to inform real-world use. Although RCTs are the ultimate source for information for evaluating products in development, they are not always feasible for rare diseases with few or no effective treatment options available. Thus, it is important to consider other measures that can help to improve the strength of evidence for cell and gene therapies targeting rare indications. While collection of PROs and other patient experience endpoints does not resolve the difficulty of conducting trials in small populations, doing so contributes empirical evidence that informs both product development and patient access. Additionally, including routine collection of PROs in registries may provide supplemental data to further characterize the benefit:risk profile of cell and gene therapies at follow-up times that would be infeasible to operationalize in a clinical trial setting.

Keywords Patient-reported outcomes · Cellular therapies · Clinical trials · CAR-T · Cancer

Introduction: Cell & Gene Therapies

Therapies derived from human cells and genes are providing novel treatment options for patients with life-threatening conditions. Gene therapies seek to modify a patient's genes to treat or cure disease. The transferred genetic material changes how a single protein or group of proteins is produced by the cell. Gene therapy can be used to reduce levels of a disease-causing version of a protein, increase production of disease-fighting proteins, or to produce new/modified proteins. Cell therapy is the transfer of intact, live cells into a patient to help lessen or cure a disease. Cell therapies alter the biological properties of living cells, either a patient's own cells as in autologous cell therapies, or from a donor as in allogeneic cell therapies, for therapeutic use. The cells used in cell therapy can be classified by their potential to transform into different cell types. Though cell and gene therapies have different mechanisms of action, the US FDA regulates both treatment modalities as gene therapies.

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Increasing the Empirical Evidence Base for Novel Cell and Gene Therapies

Both private and government payers have begun to recognize the value that PROs add to the evidence base for new therapies. Most recently, and perhaps most significantly, the Center for Medicare & Medicaid Services (CMS) sought input from an independent advisory committee, the Medicare Evidence Development & Coverage Advisory

Committee (MEDCAC), on how to incorporate existing PRO assessment tools into future clinical studies, specifically for new classes of therapies such as Chimeric Antigen Receptor T cell (CAR-T) Therapies. The 2017 FDA approvals of tisagenlecleucel and axicabtagene ciloleucel, the first two CAR-T therapies approved for cancer indications in the USA, had created a new class of commercially available cell and gene therapies and, importantly, a potential unmet need for payer review and guidance due to the expected curative benefit and likely high costs associated with both approved products. The MEDCAC meeting was convened as part of the May 2018 announcement that CMS would conduct a National Coverage Determination (NCD) for CAR-T used to treat advanced cancer in Medicare patients [2, 3]. As autologous cell therapies (including CAR-Ts and also emerging technologies such as TCR-based therapies) are individualized per patient, robust clinical trial data are difficult to obtain. These challenges are amplified among Medicare patients, who by simple life expectancy may not experience the same duration of survival as younger patients. CMS was interested in how PRO assessment tools could support health outcomes research and, consequently, coverage determinations following the approval of the first CAR-T therapies. MEDCAC panel unanimously recommended inclusion of PROs in the NCD.

The NCD for CAR-T was ultimately published on August 7, 2019, without the requirement for PRO collection as part of a larger administrative effort to recognize the significance of the curative potential of these new treatments and to encourage broad access to them (coverage with evidence development and collection of PROs were removed to avoid any potential burden placed on providers created by reporting requirements) [4]. However, the inclusion of PRO collection in the proposed NCD by CMS did signal a recognition of the importance and usefulness of PROs to enhance the empirical evidence base and our understanding of the long-term value for cell and gene therapies.

Recommendations

A multi-stakeholder group convened by Friends of Cancer Research (*Friends*), in response to the proposed NCD, met regularly in late 2018/early 2019 to consider inclusion of PROs as a factor in coverage decisions for CAR-T therapies, particularly where they pertain to breakthrough designated therapies and where investigational CAR-Ts have the potential to significantly improve health-related quality of life. This group of recognized subject-matter experts in their field included clinicians, academics, and industry representatives with extensive expertise in PROs and/or CAR-T clinical trials, and deep understanding of the requirements for US and EU drug approval applications. The collective expertise of the working group members, supported by available literature, were leveraged for the development of a PRO collection framework, focused on the core concepts of interest most relevant to patients under treatment, that could inform future payer decisions. While developed with respect to the recent CAR-T approvals and announcement of a NCD by CMS, this framework is expected to be applicable for evidence development across cell and gene therapies, and in rare diseases with moderate survival expectations.

PRO Assessment of CAR-T Therapies

Key data elements for PRO assessment are described in Table 1. PRO measures should be selected that are most appropriate to address relevant questions at the applicable timepoint related to first dose. We suggest this be divided into 3 phases: acute, sub-acute, and long term (Fig. 1). Inclusion of the acute phase collection is vital, since a lag in PRO collection after treatment initiation will miss immediate toxicity associated with the acute phase of treatment (neurological toxicity and cytokine release syndrome). We encourage consistent collection before, during and immediately following active treatment to most accurately assess the patient experience during the acute and sub-acute phases. Further, because of the curative expectations of cell therapies, multi-year follow-up should be considered to capture long-term events associated with CAR-Ts and other cell and gene therapies (FDA approval for both CAR-Ts included 15 year follow-up post-market requirements) and to assess long-term health-related quality of life; a metric which will be of increasing importance as these therapies become a new treatment paradigm [5–8]. As such, we encourage long-term follow-up timepoints, a minimum of 5 years, such that it aligns with the long-term patient experience and timeframe for projected efficacy benefits and sponsor regulatory commitments for surveillance. For monitoring of late toxicities, an approach in which immediate post-treatment questionnaires are administered monthly during the initial 6 months, then spaced out every 6 months for three years, and then annually, is consistent with commonly used approaches [9, 10]. In contrast, during active therapy, weekly PRO collection is more appropriate. For all phases of PRO assessment quantitative, rather than qualitative assessment is standard and less subject to heterogeneity or bias where multiple interviewers may be involved in administration over time.

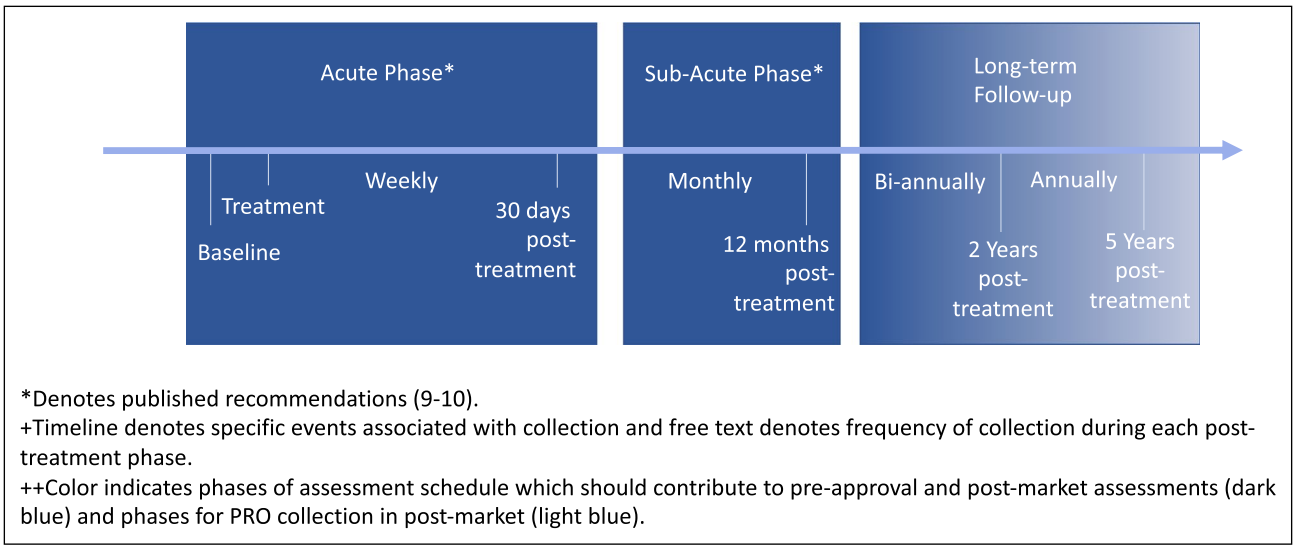
To enable researchers to systematically include the concepts of interest in a standardized manner, Table 2 was constructed which lists potential cell and gene therapy side effects, their timing in the course of treatment, and their corresponding well-defined measurement system and scoring to facilitate the integration of these tools into research in a consistent manner [11–16]. Tools proposed by MEDCAC and most frequently used within sponsor trials were included.

Table 1 Key Data Elements to Assess Chimeric Antigen Receptor (CAR) T Cell Therapy and Patient-Reported Outcomes.

Source	Clinical Outcome	Utility of Elements	Timing of Collection
Efficacy data	Response rate (RR)	Need to demonstrate efficacy using well recognized end-points	Pre-approval
	Progression free survival (PFS)		Pre-approval
	Overall survival (OS)		Post-market
Clinician-derived Safety/tolerability	Common Terminology Criteria for Adverse Events (CTCAE)	Traditionally used signals of adverse reactions/tolerability; reported by the clinician/healthcare professional; remain important for determining tolerability and should continue to be routinely captured	Pre-approval and post-market
Patient-derived Adverse event data	Symptomatic adverse events Global side effect impact/bother/burden Global health status	Suitable PRO tools should be selected that capture patient-derived data concerning the impact of the adverse events of the therapy and the overall treatment burden for the patient	Pre-approval and post-market
Additional supportive patient-derived data	Physical function	Depending on the objectives of the study and the type and intensity of therapy (including known adverse events of special interest), other elements may contribute to defining the tolerability of a treatment regimen	Pre-approval and post-market
	Other functional domains (e.g., emotional, social, role, cognitive)		
	Specific key symptoms of disease (e.g., pain, fatigue, nausea, vomiting, anorexia) as single items or composite scale		
Healthcare utilization	Hospitalization rates/duration	These items may provide a more holistic healthcare view of the tolerability of a treatment for a patient and may help determine the requirements for managing medical needs	Post-market
	Emergency department visits		
	Supportive care medication use		

Table adapted from a Friends of Cancer Research whitepaper: https://www.focr.org/sites/default/files/Comparative%20Tolerability%20Whitepaper_FINAL.pdf.

CAR, chimeric antigen receptor; CTCAE, Common Terminology Criteria for Adverse Events; PFS, progression free survival; RR, response rate; OS, overall survival.



*Denotes published recommendations (9-10).
+Timeline denotes specific events associated with collection and free text denotes frequency of collection during each post-treatment phase.
++Color indicates phases of assessment schedule which should contribute to pre-approval and post-market assessments (dark blue) and phases for PRO collection in post-market (light blue).

Figure 1 Assessment Schedule for PRO Collection.+, ++.

The Patient-Reported Outcomes Measurement Information System (PROMIS), another of the MEDCAC recommended tools, is used for monitoring patient physical, mental, and social well-being. Given that it can be administered via computer-adapted technologies and its extensive library of items, it was not included here.

Data Collection Infrastructure

Given that CAR-T administration is limited to a select number of specialized clinical locations by the Risk Evaluation and Mitigation System required by FDA, PRO data reporting is expected to be relatively straightforward during the acute phase of treatment. However, the extended assessment periods recommended in this commentary will expand data reporting requirements into different care settings. Researchers, CMS, and other payers will need to be mindful when developing methodologies and policies to account for potential disruptions in data collection as patients transition from hospital inpatient to out-patient settings or from academic medical centers back into routine care as a standard infrastructure to seamlessly collect this data from clinic to routine care is currently lacking. Oncologists in routine practice, including standard practice and community oncology practices, are less likely to have experience with PRO collection and fewer resources to devote to administration of PRO instruments. There are a variety of third-party vendors and real-world evidence suppliers to support the extended assessment requirements and reduce financial and resource burdens placed on practices in those settings and increase collection compliance. When assessing an appropriate vendor, availability of patients, sites that are accessible in the third-party system, the comprehensiveness of the clinical record (e.g., clinical outcomes), integration of patient facing symptom collection capabilities, quality of the design of the use experience, and impact of symptom collection processes on the health system practice, and analytic capabilities are key factors to consider. Mobile health monitoring and electronic data collection (ePRO) should also be encouraged as it may facilitate real-time monitoring of compliance for backup data collection and easy data transfer. The ability to utilize ePRO will be particularly important for collecting data on late toxicities or as patients are transferred to out-patient settings. Further, ePRO systems may provide more flexible platforms for customizable data collection, though not necessarily appropriate for all studies or patient populations and additional cost may be a complication to their use [17]. A number of vendors offer stand-alone ePRO software for data collection, and increasingly electronic health record (EHR) systems and real-world evidence companies offer tools for collection of PRO data within the EHR or accompanying patient portals. Patient registries are identified as another source of real-world data that can be used to generate RWE in the Framework for FDA's Real-World Evidence Program and are particularly useful in data collection for rare diseases [18, 19]. Looking forward, more integration of standard patient outcomes into the medical record and routine care not only for cell and gene therapies but across also cancer treatments should be a priority for both regulator, payers, providers and health systems.

Use of PROs to Inform Coverage Determinations

Considering that cell therapies, such as CAR-Ts, are expected to extend median overall survival (OS) by a number of years, well beyond the usual scope of a clinical trials,

Table 2 CAR-T Applicable PROs and Their Representation in MEDCAC-Approved Tools.

Concepts	Symptom	Acute	Sub-acute	Long Term (1 + years)	Item	Response Format, Basic Scoring
Adverse events (AE)/toxicity						
AE/GI	Nausea	X	X		EORTC: Have you felt nauseated? MDASI: Your nausea at its WORST? PRO-CTCAE: Nausea	4 point (pt) Likert scale, scored as single item 11 point NRS F(Frequency), S (severity)
	Vomiting	X	X		EORTC: Have you vomited? MDASI: Your vomiting at its WORST? PRO-CTCAE: Vomiting	4 pt Likert scale, scored as single item 11 point NRS F, S
	Diarrhea	X	X		EORTC: Have you had diarrhea? PRO-CTCAE: Diarrhea MDASI: Your diarrhea at its WORST?	4 pt Likert scale, scored as single item F 11 point NRS
	Constipation	X	X		EORTC: Have you been constipated? PRO-CTCAE: Constipation MDASI: Your constipation at its WORST?	4 pt Likert scale, scored as single item S 11 point NRS
	Anorexia	X	X		EORTC: Have you lacked appetite? MDASI: Your problem with lack of appetite at its WORST? PRO-CTCAE: Decreased appetite	4 pt Likert scale, scored as single item 11 point NRS S, I (Interference)
AE/CRS	Fever, Chills	X	X		PRO-CTCAE: Chills Increased sweating Hot flashes Heart palpitations MDASI: Your fever or chills at its WORST? Your feeling of malaise (not feeling well) at its WORST?	F, S F, S F, S F, S 11 point NRS 11 point NRS
	Edema	X	X		EORTC: Have you experienced any swelling in certain parts of your body (e.g., ankles, legs or around your eyes)? PRO-CTCAE: Swelling MDASI: Your swelling of your hands, legs, feet, abdomen, or around your eyes at its WORST? Your problem with ankle swelling at its WORST?	4 pt Likert scale, scored as single item F, S, I 1 point NRS 11 point NRS
AE/Constitutional	Fatigue	X	X	X	EORTC: Were you tired? MDASI: Your fatigue (tiredness) at its WORST? Your problem with lack of energy at its WORST? PRO-CTCAE: Fatigue	4 pt Likert scale, scored as single item 11 point NRS 11 point NRS S, I

Table 2 (continued)

Concepts	Symptom	Acute	Sub-acute	Long Term (1 + years)	Item	Response Format, Basic Scoring
	Myalgia	X	X		EORTC: Have you felt weak? Have you had pain? Did pain interfere with your daily activities? PRO-CTCAE: Muscle pain MDASI: Your muscle weakness at its WORST? Your muscle soreness or cramping at its WORST?	4 pt Likert scale, scored as single item F, S, I 11 point NRS 11 point NRS
	Arthralgia	X	X		EORTC: Have you had pain? Did pain interfere with your daily activities? PRO-CTCAE: Joint Pain MDASI: Your joint stiffness or soreness at its WORST?	4 pt Likert scale, scored as single item F,S,I 11 point NRS
AE/CNS	Headache	X	X		PRO-CTCAE: Headache MDASI: Your headache at its WORST?	F,S,I 11 point NRS
	Tremor	X	X			
	Dizziness	X	X		PRO-CTCAE: Dizziness	S, I
	Confusion	X	X		EORTC: Have you had difficulty remembering things? PRO-CTCAE: Concentration Memory MDASI: Your problem with remembering things at its WORST?	4 pt Likert scale, scored as single item S,I S,I 11 point NRS
	Aphasia	X	X		EORTC: Have you had trouble finding the right words to express yourself? Did you have difficulty speaking? Did you have trouble communicating your thoughts? MDASI: Your difficulty speaking (finding the words) at its WORST?	4 pt Likert scale, scored as part of a 3 item communication deficit sub-scale 11 point NRS
	Insomnia	X	X		EORTC: Have you had trouble sleeping? PRO-CTCAE: Insomnia MDASI: Your disturbed sleep at its WORST?	4 pt Likert scale, scored as single item S, I 11 point NRS

Table 2 (continued)

Concepts	Symptom	Acute	Sub-acute	Long Term (1 + years)	Item	Response Format, Basic Scoring
	Anxiety	X	X		EORTC: Did you feel irritable? Did you feel depressed? Did you feel tense? Did you worry? MDASI: Your feeling of being distressed (upset) at its WORST? Your feeling sad at its WORST? PRO-CTCAE: Anxious Discouraged Sad	4 pt Likert scale, scored as single item 11 point NRS 11 point NRS F, S, I F, S, I F, S, I
AE/respiratory	Dyspnea	X	X		EORTC: Were you short of breath? three item scale: [1] Were you short of breath when you rested? [2] Were you short of breath when you walked? [3] Were you short of breath when you climbed stairs? PRO-CTCAE: Shortness of breath MDASI: Your shortness of breath, at its worst?	4 pt Likert scale, scored as single item 4 pt Likert scale, scored as multi-item sub-scale S, I 11 point NRS
	Cough	X	X		EORTC: How much did you cough? PRO-CTCAE: Cough MDASI: Your coughing at its WORST?	4 pt Likert scale, scored as single item. S, I 11 point NRS
General symptom (disease or treatment)	Pain	X	X	X	EORTC: Have you had pain? Did pain interfere with your daily activities? PRO-CTCAE: General pain Muscle pain Joint pain MDASI: Your pain at its WORST?	4 pt Likert scale, scored as single item. F, S, I F, S, I F, S, I 11 point NRS

Table 2 (continued)

Concepts	Symptom	Acute	Sub-acute	Long Term (1 + years)	Item	Response Format, Basic Scoring
Physical function		X	X	X	(EORTC) Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? Do you have any trouble taking a *long* walk? Do you have any trouble taking a *short* walk outside of the house? Do you need to stay in bed or a chair during the day? Do you need help with eating, dressing, washing yourself or using the toilet? MDASI Interference scale[a] items: Walking Activity Working (including housework) Relations with other people Enjoyment of life Mood	4 pt Likert scale, scored as single sub-scale 11 point NRS
Instrumental activities of daily living (IADLs)		X	X	X	Role Function (EORTC) Were you limited in doing either your work or other daily activities? Were you limited in pursuing your hobbies or other leisure time activities? MDASI Interference scale[a]	4 pt Likert scale, scored as single sub-scale 11 point NRS
Social functioning		X	X	X	EORTC: Has your physical condition or medical treatment interfered with your *family* life? Has your physical condition or medical treatment interfered with your *social* activities? MDASI Interference scale[a]	4 pt Likert scale 11 point NRS
Financial		X	X	X	Has your physical condition or medical treatment caused you *financial* difficulties?	4 pt Likert scale

As part of this work, the PRO subject-matter experts on the multi-stakeholder group drafted this comprehensive table mapping concepts relevant to CARTs, cell and gene therapies to their respective and most commonly used PRO tools also endorsed by CMS for evidence generation (e.g., PRO-CTCAE, EORTC, and MDASI).

[a]The items from the interference scale capture interference with daily living caused by these symptoms.

AE, adverse events; CNS, central nervous system; CRS, cytokine release syndrome; EORTC, European Organization for Research and Treatment of Cancer; F, frequency; GI, gastrointestinal; I, interference; IADLs, instrumental activities of daily living; MDASI, MD Anderson Symptom Inventory; NRS, numeric rating scale; PRO-CTCAE, Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; pt, point; S, severity.

it will be essential to support ongoing evaluation of these products in the post-market setting. Ongoing evaluation will be particularly relevant as the current approved CAR-T products rapidly expand their labels into new indications and patient populations. Tisagenlecleucel-t, first approved in August 2017 for relapsed and refractory pediatric and young adult patients with B cell acute lymphoblastic leukemia (ALL), received a May 2018 label expansion for use in diffuse large-B cell lymphoma, a type of non-Hodgkin's lymphoma occurring most frequently in individuals over 60 years of age. PROs will be a metric to consider in this ongoing surveillance to ensure a holistic approach to performance evaluations, including:

1. Determining appropriate patient populations;
2. Expanding indications;
3. Considering new care settings, and;
4. Informing long-term value.

PROs will be metrics for informing coverage as new patient populations and new uses of CAR-T cell therapies are identified. However, since the long-term effects of CAR-T cell therapies are expected to last years, well beyond the acute phase as the patient transitions back into routine care, the impact of treatment setting will also be relevant to studying long-term effects and should be included as a consideration in PRO collection requirements. Therefore, we support the collection of PRO information in both the out-patient and inpatient settings and in routine practice. In addition, given the novelty of these therapies, we believe that the REMS restrictions provide a unique opportunity to collect clinician reported and patient-reported outcomes, as the conclusions from each may not necessarily be the same. Further, special considerations will be needed due to the individualized nature of CAR-T-therapy manufacturing. Specifically, little is currently being collected to assess the potential impact that product or process changes have on health outcomes. PRO data could be used to monitor technology progression for changes in patient experience and health outcomes that may not otherwise be identifiable due to the extended timeline of surveillance and coordinated data-sharing infrastructure needed. As the manufacturing process is improved and yields safer, more efficacious therapies and evidence evolves to demonstrate the value of cellular therapy over other treatment options, this may change patient/provider calculations and shared medical decision-making.

Conclusions

Integration of this framework into coverage decisions will require identification of key PRO measures for value assessments and development of standards to ensure they are uniformly collected and obtained from well-defined PRO instruments. Once quality standards and methods for integrating PRO measures with traditional clinical trial measures have been developed, PROs can be systematically included to increase the evidence base for these new therapies [20]. Additionally, PRO measures provide data that are integral to comprehensive disease modeling using health-related quality of life (HRQoL) metrics and values. Efforts to improve disease modeling for CAR-T therapies are ongoing; these models risk inaccuracy without the ability to include long-term toxicity and HRQoL data. When incorporating PROs, it will be important to delineate the research objective and endpoints in the study, as this will affect the PRO tools selected and the methodology employed.

Notes

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Author Contributions

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Compliance with Ethical Standards

Conflict of interest

Dr. Basch reports grants from the National Cancer Institute and the Patient Centered Outcomes Research Institute, outside the submitted work; and Dr. Basch is on the Editorial Board of the Journal of the American Medical Association and consults on research projects at Memorial Sloan Kettering Cancer Center, Dana Farber Cancer Institute, Centers for Medicare & Medicaid Services, and Research Triangle Institute. Dr. Basch is a Scientific Advisor for Sivan Healthcare, CareVive Systems, and Navigating Cancer. Authors Laura Lasiter, Alicyn Campbell, Stacie Hudgens, Mark Stewart, James J. Wu, Allison Barz Leahy, and Jeff Allen have nothing to disclose.

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