NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 12/01/2022
To: "Huda Al-Kouatly" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1845

RE: Manuscript Number ONG-22-1845

Implications for prenatal genetic testing after reversal of Roe v. Wade in the United States

Dear Dr. Al-Kouatly:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

The Editors would be willing to consider your revised version for online fast-track publication if you can return your updated manuscript to us quickly.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

We will expect your revision by 12/08/2022. If you need additional time, please contact the Editorial Office (em@greenjournal.org) to request an extension.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figures 1-2: Please confirm that these figures were created with data from the listed sources, and the figures do not mirror figures already published.

REVIEWER COMMENTS:

Reviewer #1:

Obstetrics and Gynecology
Manuscript number: ONG-22-1845
"Implications for prenatal genetic testing after reversal of Roe v. Wade in the United States"

General:
The submitted commentary article describes contemporary options for fetal aneuploidy screening and invasive diagnostic techniques in relation to current gestational age-related restrictions on pregnancy termination in the United States.

1. The manuscript is very articulate and topical.

2. Consider avoiding judgmental speculation on potential further restrictions on pregnancy termination (i.e. Lines 178-179: "…10 of 35 states have the current status threatened…") and instead state "legal challenges to current statues are pending in 10 of 35 states" or similar; in this manner the article maintains a scientific basis and avoids straying into political commentary.

3. Did the authors consider invasive testing results in the context of FISH (fluorescent in-situ hybridization) studies, which can often give a preliminary answer in 24-48 hours? (Table 1)

4. Consider inclusion of "early" fetal anatomic survey ultrasound (12-14 weeks) as a potential component of fetal anomaly screening in more restrictive locales.

5. Recognizing duplication will occur, I would suggest expanding Table 1 to include (individually) all 50 states.

6. I find Figure 1 to be confusing:
a. Fetal anatomic screening sonography is typically performed at 18-20 weeks in my institution (not 20 weeks until term as listed).
b. Consider including a bar on "early" fetal anatomic screening sonography from 12-14 weeks (or similar).

Reviewer #2:

Manuscript # ONG-22-1845 is a nice primer on the current state of prenatal genetic testing and counseling as they relate to abortion access since the Dobbs vs. Jackson's Women's Health Organization Decision was handed down. The essay is clear, well-written, accurate, and mostly free of bias. It is well-researched and impressive in its comprehensiveness, covering multiple contingencies that obstetrical care providers and genetic counselors in certain states might encounter in these unfamiliar environments while helping guide their patients through the decision-making process. The information in this manuscript provides a great foundation for a Grand Rounds-type lecture or a stand-alone ACOG or CREOG monograph. Questions, comments, suggestions follow:

1. In the Abstract (lines 44-46) and subsequently (lines 156-157) the authors describe 13 states with total bans on abortion "in addition to," 7 states that prohibit abortion when the fetus is found to have a genetic abnormality. This implies a total of 20 states that have either total abortion bans or bans when a fetus has a genetic abnormality. A careful review of Tables 1 and 2, however, demonstrates substantial overlap between these 2 categories; North Dakota and Ohio are the only states without complete restriction that prohibit abortion specifically for a fetal genetic abnormality. More accurately, among the 13 states with total abortion bans, 5 prohibit abortion specifically for a fetal abnormality (although I am not sure why this specific ban would be necessary for states that already have a total ban), and an additional 2 states prohibit abortion when the fetus has a genetic abnormality.

2. The point above might also be made more clearly if Table 2 were revised to include Alabama, Idaho, Texas, and Wisconsin and changing the title to "States with bans or proposed bans for fetal indications," and have a new column to identify the 13 states with outright bans.

3. In line 129, when describing state-specific exceptions to abortion bans, consider adding the phrase "serious risk to the mother's life" to rape and incest.

4. In line 234, the term, "substandard care" is vague. Please list specific examples of how care can become substandard for women with transportation limitations who live in states with gestational age restrictions on abortion.

Reviewer #3: This is a timely and important comment. A few minor comments below.

1. While traditional screening has focused on common aneuploidies, there is increasing use of expanded carrier screening and first trimester ultrasound which may identify fetal genetic syndromes. Additionally for patients under the age of 35 the risk of a clinically significant CNV is higher than that for common aneuploidy, but will not be picked up with NIPS. Consider adding some discussion about how the expansion of genetic testing options will be impacted by the restrictions, as many of the diagnosis cannot be completed in the first trimester.

2. Given recent elections, make updates to tables as needed.

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Sincerely,
Ebony B. Carter, MD, MPH
Associate Editor, Equity

The Editors of Obstetrics & Gynecology

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://nam10.safelinks.protection.outlook.com/?url=https%3A%2F%2Fjournals.lww.com%2Fgreenjournal%2FDocuments%2FRevisionChecklist_Authors.pdf&data=05%7C01%7CMegan.Raymond%40jefferson.edu%7C7d971c970d874e57d4ab08dad3d735af%7C55a89906c710436bbc444c590cb67c4a%7C0%7C0%7C638055218513456196%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=kf%2FzdeqGF0c%2B3aQ8wZclzBi5AsiuhyhfHGtysAE%2Frbk%3D&reserved=0and making the applicable edits to your manuscript.

Response: We thank you for your careful review of our paper and the opportunity for fast-track online publication. The authors confirm that the revised manuscript included the applicable edits as outlined in the Revision Checklist.

* Figures 1-2: Please confirm that these figures were created with data from the listed sources, and the figures do not mirror figures already published.

Response: We can confirm that both Figure 1 and Figure 2 are original figures created by the authors without mirroring previously published figures. The data used in the figures are from the sources cited, and we amended the figure legend to reflect this.

NOTE

The authors have included several references in order to respond to the reviewer comments. They are included in a works cited at the end of this document, as well as added to the manuscript.

The page and line numbers cited in this document reflect the page numbers when the manuscript is viewed with the tracked changes hidden.

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We thank you for this comment.

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Response: Thank you for your helpful feedback. We have updated the language used to maintain a clear scientific basis, as suggested by the reviewer. We have also updated the current status of abortion restriction in each state throughout the manuscript, as documented in tracked changes in our revised manuscript, to be accurate as of 12/11/2022 since the results of the 2022 election.

Proposed change:
Page 8, Line 200: "As of December 11, 2022, 14 states have restrictions under which no diagnostic testing could be completed in time for a patient to terminate the pregnancy legally. Thirty-five states, including Washington D.C., permit abortion up to or exceeding gestational ages that would allow for both CVS and amniocentesis prior to obtaining a legal in-state abortion. One of these states, Utah, has an 18-week gestational age ban under which obtaining amniocentesis results prior to the gestational age limit may be challenging from a logistical perspective. Eight of these 35 states currently have pending legal challenges to statutes protecting abortion access."

3. Did the authors consider invasive testing results in the context of FISH (fluorescent in-situ hybridization) studies, which can often give a preliminary answer in 24-48 hours? (Table 1)

Response: Thank you for raising this important consideration. We have added a short discussion on varying laboratory techniques used for diagnostic testing of fetal samples including karyotype, microarray, and FISH. Our brief overview of screening and diagnostic genetic testing methods highlights the strengths and limitations of each of these techniques, including FISH.

Proposed Change:
Page 4, Line 118: "There are several laboratory techniques to analyze fetal samples, including karyotype, chromosomal microarray (CMA), and fluorescent in-situ hybridization (FISH). Karyotype and CMA are both considered diagnostic tests to identify chromosomal aneuploidy. CMA also can identify copy number variants and is recommended when fetal structural anomalies are identified. Result turnaround times for both karyotype and CMA vary, but take approximately 2 weeks. FISH can identify limited aneuploidies (Trisomy 21, 18, 13, and sex chromosomes) and can provide more rapid results within 24-48 hours. However, it is still considered a screening test rather than a diagnostic result[1]."

Page 10, Line 266: "Laboratory screening techniques with quicker turnaround times, such as FISH, may also be increasingly used in addition to the standard karyotype or microarray in this current climate."

4. Consider inclusion of "early" fetal anatomic survey ultrasound (12-14 weeks) as a potential component of fetal anomaly screening in more restrictive locales.

Response: Thank you for this helpful feedback. The authors agree with the reviewer's assessment that patients in more restrictive states could benefit from clinicians and institutions adopting more first-trimester and early second-trimester anatomy assessments and adapting protocols to this point.

We addressed this on page 9, Lines 241, “Early fetal anatomic assessment has been found to be beneficial for the diagnosis of structural abnormalities at less than 16 weeks [2]. With the increasing evidence for the utility and performance of first-trimester anatomy ultrasound over the past decade, clinicians and medical institutions may consider adopting first-trimester and early second-trimester anatomy ultrasound protocols [3, 4] to provide patients with more information prior to a gestational age ban in their state.”

We have also added “Early Fetal Anatomy Assessment” to Figure 1 in our timeline.

5. Recognizing duplication will occur, I would suggest expanding Table 1 to include (individually) all 50 states.

Response: Thank you for this helpful suggestion. We have changed Table 1 to include all 50 states individually and updated the formatting in accordance with the Editors’ checklist.

6. I find Figure 1 to be confusing:
a. Fetal anatomic screening sonography is typically performed at 18-20 weeks in my institution (not 20 weeks until term as listed).

Response: Thank you for your feedback. We have updated the figure to reflect that routine fetal anatomy screening ultrasound is generally offered at 18-22 weeks[5, 6]. We have also included a footnote to clarify that an anatomy ultrasound could be performed up to term for patients who are late to prenatal care; however, the views may be suboptimal and limited at a later gestational age.

Footnote: Fetal anatomy ultrasound screening is recommended between 18-22 weeks. While it can be performed later in gestation for patients late to prenatal care, the images obtained may be suboptimal and limited.

b. Consider including a bar on "early" fetal anatomic screening sonography from 12-14 weeks (or similar).

Response: Thank you for this suggestion. We have updated Figure 1 to include early fetal anatomic assessment from 11-14 weeks.

Reviewer #2:

Manuscript # ONG-22-1845 is a nice primer on the current state of prenatal genetic testing and counseling as they relate to abortion access since the Dobbs vs. Jackson's Women's Health Organization Decision was handed down. The essay is clear, well-written, accurate, and mostly free of bias. It is well-researched and impressive in its comprehensiveness, covering multiple contingencies that obstetrical care providers and genetic counselors in certain states might encounter in these unfamiliar environments while helping guide their patients through the decision-making process. The information in this manuscript provides a great foundation for a Grand Rounds-type lecture or a stand-alone ACOG or CREOG monograph. Questions, comments, suggestions follow:

1. In the Abstract (lines 44-46) and subsequently (lines 156-157) the authors describe 13 states with

total bans on abortion "in addition to," 7 states that prohibit abortion when the fetus is found to have a genetic abnormality. This implies a total of 20 states that have either total abortion bans or bans when a fetus has a genetic abnormality. A careful review of Tables 1 and 2, however, demonstrates substantial overlap between these 2 categories; North Dakota and Ohio are the only states without complete restriction that prohibit abortion specifically for a fetal genetic abnormality. More accurately, among the 13 states with total abortion bans, 5 prohibit abortion specifically for a fetal abnormality (although I am not sure why this specific ban would be necessary for states that already have a total ban), and an additional 2 states prohibit abortion when the fetus has a genetic abnormality.

Response: Thank you for your careful evaluation of the manuscript. We will remove the language "in addition to" in order to be more precise in our presentation of current restrictions. We have updated the manuscript to clarify where there is overlap in states with total abortion bans, as well as specific bans on termination for fetal genetic abnormalities.

Proposed Change:
Page 2, Line 58: Seven states specifically prohibit abortion for fetuses with a genetic abnormality.

Page 7, Line 180: "Of the 13 states with total bans on abortion, five have specific legislation prohibiting abortion when the fetus is found to have an abnormality. An additional two states, North Dakota and Ohio, prohibit abortion for a fetus with an abnormality." (Table 2).

2. The point above might also be made more clearly if Table 2 were revised to include Alabama, Idaho, Texas, and Wisconsin and changing the title to "States with bans or proposed bans for fetal indications," and have a new column to identify the 13 states with outright bans.

Response: Thank you for this suggestion. We have modified Table 2 to highlight states that, in addition to bans on terminations for fetal abnormalities, have also introduced outright bans.

Table 2. States with bans or proposed bans on abortion for fetal indications

State	Abortion Prohibited for Fetal Abnormality	Proposed Prohibition	Perinatal Hospice Counseling Required
Arizona		X	X
Arkansas*		X	
Indiana		X	
Kansas			X
Kentucky*		X	
Louisiana*		X	
Minnesota			X
Mississippi*	X		
Missouri*	X		
North Dakota	X		
Ohio	X		
Oklahoma*			X
South Dakota*	X		
Tennessee*	X		
West Virginia*	X		

*states with total or near-total abortion bans as of December 11th, 2022

3. In line 129, when describing state-specific exceptions to abortion bans, consider adding the phrase "serious risk to the mother's life" to rape and incest.

Response: Thank you for your suggestions, we have updated the text to reflect this suggestion.

Proposed Change:
Page 6, Line 156: "In the case of complete bans, these states do not legally permit any pregnancies to be terminated outside of state-specific exceptions such as cases of rape, incest, or serious threat to maternal life."

4. In line 234, the term, "substandard care" is vague. Please list specific examples of how care can become substandard for women with transportation limitations who live in states with gestational age restrictions on abortion.

Response: Thank you for this helpful comment. We have added specific examples in the discussion to clarify what we mean by "substandard care" in order to illustrate the inequities women with transportation limitations face.

Proposed Change to Conclusion:
Page 11, Line 272: "Interventions that can be completed at an earlier gestational age, such as CVS and early fetal anatomy assessment, may be increasingly utilized in states with earlier gestational age bans. In addition, patients without the means to travel out of state for a termination procedure may disproportionately receive substandard care, such as being forced to continue a pregnancy they would otherwise choose to terminate. Clinicians may also be placed in the suboptimal position of counseling these patients on the option of termination based on screening tests alone."

Reviewer #3: This is a timely and important comment. A few minor comments below.

1. While traditional screening has focused on common aneuploidies, there is increasing use of expanded carrier screening and first trimester ultrasound which may identify fetal genetic syndromes. Additionally for patients under the age of 35 the risk of a clinically significant CNV is higher than that for common aneuploidy, but will not be picked up with NIPS. Consider adding some discussion about how the expansion of genetic testing options will be impacted by the restrictions, as many of the diagnosis cannot be completed in the first trimester.

Response: Thank you for your thoughtful comments and helpful feedback. We agree that genetic screening and evaluation beyond common aneuploidies is an important consideration in prenatal care today and impacted by the current legislation. We have added the following to our discussion to reflect these considerations.

Regarding first-trimester ultrasound, please see our response to Reviewer 1's comment #4 about early fetal anatomy ultrasound assessment.

Regarding patients under 35, on page 9, line 226, we have clarified that by young patients, we mean patients under 35, and we further clarified that NIPS would not pick up the CNVs that they are at greater risk for.

Regarding expanded carrier screening and the expansion of genetic testing options available, we have updated the text to reflect this concern.

Proposed changes:
Page 5, Line 134: "A discussion regarding expanded carrier screening is outside the scope of this opinion, but it is available in both preconception and prenatal care. Technological advances in DNA sequencing and analysis have allowed for the development of large screening panels for a large number of conditions at once[7]. Other genetic testing options available in preconception care include pre-implantation genetic testing of embryos for aneuploidy (PGT-A) and single gene mutations (PGT-M)[8]."

Page 9, Line 225: "For example, patients younger than 35 years may opt for NIPS in order to receive results at an earlier gestational age, even though they are at higher risk for a clinically significant CNV that wouldn't be identified with NIPS. This would have several consequences, including a higher false positive rate for aneuploidy because of their young age, as well as potentially missing the opportunity to screen for other genetic abnormalities and clinically significant CNVs that may be identified with another screening paradigm, such as sequential screen[9].

Page 9, Line 232: "Diagnostic testing by chromosomal microarray is required for diagnosis of copy number variants with CVS or amniocentesis."

Page 9, Line 247: "Abortion restrictions have further potential implications for the genetic testing available in preconception care. The use of expanded carrier screening is complicated in states with early gestational age bans, as patients who screen positive as carriers may not receive their CVS or amniocentesis diagnostic results in time to make a decision regarding termination. Patients who screen positive in preconception care may choose to pursue IVF and preimplantation genetic testing for a single gene mutation (PGT-M) in order to have a definitive fetal diagnosis prior to conception. The use of personhood language in abortion bans also has a potential unintended consequence of restricting the provision and legality of fertility services such as IVF, further compounding the limited options available to patients in states with more restrictive legislation[10].

2. Given recent elections, make updates to tables as needed.

Response: We have updated our tables, map, and the body of the manuscript to reflect these changes as of December 11th, 2022. See our response to Reviewer 1's comment #2 above. We also changed our example of a state with threatened protection from Pennsylvania to Virginia, based on the results of the recent elections.

We also updated the body of the manuscript to reflect that in the creation of Table 3, we reviewed and cited individual state legislative websites and documents, in addition to the information collected by the Guttmacher Institute.

Proposed Change:
Page 6, Line 161: States with threatened protection include states like Virginia, which have pending legal challenges or judge-ordered holds on bans[11].

Proposed Change:

Page 7, Line 192: This data is presented as collected by the Guttmacher Institute as well as individual state legislative websites and documents (Table 3).

1. *Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders.* Obstet Gynecol, 2016. **127**(5): p. e108-e122.
2. Lostchuck, E., et al., *Population-based trends in invasive prenatal diagnosis for ultrasound-based indications: two decades of change from 1994 to 2016.* Ultrasound Obstet Gynecol, 2019. **53**(4): p. 503-511.
3. Harper, L.M., et al., *The Performance of First-Trimester Anatomy Scan: A Decision Analysis.* Am J Perinatol, 2016. **33**(10): p. 957-65.
4. Liao, Y., et al., *Routine first-trimester ultrasound screening using a standardized anatomical protocol.* American Journal of Obstetrics & Gynecology, 2021. **224**(4): p. 396.e1-396.e15.
5. *Practice Bulletin No. 175: Ultrasound in Pregnancy.* Obstet Gynecol, 2016. **128**(6): p. e241-e256.
6. *AIUM-ACR-ACOG-SMFM-SRU Practice Parameter for the Performance of Standard Diagnostic Obstetric Ultrasound Examinations.* J Ultrasound Med, 2018. **37**(11): p. E13-e24.
7. *Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine.* Obstet Gynecol, 2017. **129**(3): p. e35-e40.
8. *Preimplantation Genetic Testing: ACOG Committee Opinion, Number 799.* Obstet Gynecol, 2020. **135**(3): p. e133-e137.
9. Norton, M.E., et al., *Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities.* Am J Obstet Gynecol, 2016. **214**(6): p. 727.e1-6.
10. Feinberg, E.C., J.F. Kawwass, and M.I. Cedars, *Roe v Wade and the Threat to Fertility Care.* Obstetrics & Gynecology, 2022. **140**(4): p. 557-559.
11. Allison McCann, A.S.W., Ava Sasani, Taylor Johnston, Larry Buchanan, Jon Huang, Margot Sanger-Katz, Kate Zernike *Tracking the States Where Abortion Is Now Banned*. 2022.