Wisconsin Department of Health Services
Wisconsin Division of Public Health
Newborn Screening Program
CF/Molecular Subcommittee Meeting
Tuesday, November 19, 2024
10:00 a.m. - 12:00 p.m.
Zoom: https://dhswi.zoomgov.com/j/1605877302?pwd=MVZLcGNsMWhBNlpET1poUDNjSXp2Zz09

Meeting ID: 160 587 7302
Or call by location +1 669 254 5252 or +1 646 828 7666 or +1 551 285 1373 or +1 669 216 1590

Minutes

Meeting Invitees:

X	Dr. Nicholas Antos		Dr. Evan Kemp	X	Darci Pfeil
X	Dr. Mei Baker		Kristin Kruschel		Jacklyn Schlan
	Dr. Vivek Balasubramaniam		Dr. Jennifer Kwon	X	Erin Seffrood
X	Dr. Christina Barreda		Olivia Lampone	X	Becky Steinmetz
X	Anna Cisler		Alison LaPean-Kirschner	X	Dr. Robert Steiner
	Ellen Compto	X	Dr. Hara Levy		Tammy Summers
X	Kendall Davis	X	Sharon Luu		Tammi Timmler
	Dr. Joshua Freedman		Michelle McDonagh	X	Mary Marcus Walters
	Sumedha Ghate	X	Peggy Modaff		Casey Weise
	Rachael Haupt-Harrington		Dr. Kwabena Osman		Students:
X	Tami Horzewski				

Agenda:

Tuesday, November 19, 10:00 AM – 12:00 PM				
Time:	**Topic:**	**Lead:**	**Follow-up Items:**	**Notes:**
10:00-10:05	**Welcome and Review of Minutes**	Dr. Antos		Motion to approve January 30, 2024 minutes: 1st motion: Peggy Modaff 2nd motion: Dr. Mei Baker Motion approved.
10:05–10:15	**Department of Health Services (DHS)/ WI State Lab of Hygiene (WSLH)**	Tami Horzewski/ Dr. Baker		Tami Horzewski shared the following DHS Update: •Dr. Steiner is back with the NBS Program part-time in the role of DHS NBS Program Medical Director. He works

	Updates			primarily on Tuesdays and Thursdays and every other Friday. • The NBS Program is part of the Family Health Section (FHS). The new FHS Manager, Leah Eckstein, recently started and may join some future meetings. •Rulemaking for the NBS blood card fee increase and the addition of two conditions to the NBS panel, X-ALD and MPS 1, is moving through the process. The legislative report was sent to the Governor's Office and addressed the comments received during the public hearing/comment period. Rulemaking review will resume when the legislative session begins around January 2025. •A small workgroup of metabolic, neurology, and stem cell transplant specialists are currently discussing the work that would need to be done in preparation for possible screening for Infantile Krabbe Disease, the development of a care infrastructure in state, and the possibility of initial care out of state. Infantile Krabbe Disease has been recently added to the Recommended Uniform Screening Panel (RUSP). • The Title V, five year needs assessment for setting priorities for maternal and child health work is

				underway. There were focus groups and a state-wide survey. This information is being analyzed and in December will look at setting priorities for the next 5 years, 2026-2030. • DHS will be relocating to a new office building. The move is scheduled for fall of 2025. Dr. Mei Baker shared the following WSLH update: • **HRSA-23-065: State Newborn Screening Priorities Program (NBS Propel)** – **Specific Aim 1:** Expand testing capability to improve laboratory readiness for screening Mucopolysaccharidosis types I and II (MPS I and MPS II), and Guanidinoacetate Methyltransferase (GAMT) deficiency.—Guanidinoacetate assay evaluation is completed. – **Specific Aim 2:** Improve NBS specimen transit time via increasing transparency and effective communication.—Ongoing – **Specific Aim 3:** Establish a system and a process to monitor spinal muscular atrophy

				screening positive infants and assess treatment efficacy. – It is in progress to establish a REDCap-based 5 year SMA follow-up database and associated dashboard • **X-ALD Demonstration Project Implementation** – Total screened newborns: 59,123 (9/20/2023 – 9/19/2024) – Reported screen positive: 6 male and 8 female – Confirmed: 5 male (including 1 ZWS) and 5 female – Other outcomes: 2 false positive (1 male and 1 female) 1 further clinical follow up declined (known carrier mother) 1 pending (female) • **CAP Self-Inspection** – The NBS lab underwent a successful Self-CAP inspection on October 30, 2024. No major

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				testing concerns with minor house-keeping issues **New Staff Member**: Sharon Luu started as the NBS Follow-Up Manager on 10/28/2024. She will provide future CF screening summaries for the subcommittee meetings.
10:15 – 10:30	**2023 Screening Summary**	Dr. Baker		Dr. Baker shared the following 2023 Screening Summary: There were 59,067 newborns screened. Confirmed CF and CRMS – 15 (8 CF/7 CRMS) Confirmed SMA - 6
10:30 – 10:40	**CFTR2 updated CFTR variant list**	Dr. Baker	?Why not against LTD rule? Question: Elevated sweat test, call back?	The current CFTR panel has 689 variants and can be expanded to 981 CF-causing variants. Because of the new FDA LDT rules, we cannot change our current 689 variant panel, but we can benefit from the updated list when we reanalyze the CFTR NGS assay results using an existing process. All specimen with top 4% daily IRT undergo 689 CFTR variant panel analysis, and specimens with one variant will further undergo CFTR reanalysis. Only specimens with two CF-causing variants will be reported as CF screening positive.

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				<table><tr><th></th><th>V1 4/2012</th><th>V2 7/2013</th><th>V3-V13</th><th>V14 4/2023</th><th>V15 8/2024</th></tr><tr><td>Number of Patients</td><td>35,312</td><td>39,696</td><td></td><td>89,052</td><td>112,935</td></tr><tr><td>CF-causing</td><td>123</td><td>175</td><td></td><td>719</td><td>1,085</td></tr><tr><td>Varying Clinical Consequence</td><td>15</td><td>12</td><td></td><td>49</td><td>55</td></tr><tr><td>Non CF-causing</td><td>5</td><td>10</td><td></td><td>25</td><td>27</td></tr><tr><td>Unknown Significance</td><td>15</td><td>6</td><td></td><td>11</td><td></td></tr><tr><td>Total</td><td>158</td><td>203</td><td></td><td>804</td><td>1,167</td></tr></table> Discussion: How to do that? When?
10:40 – 11:40	**New CFF NBS Guidelines and NACFC Updates**	Dr. Baker/Dr. Antos/All	Laboratory/clinical/implementation	**Dr. Baker presented the following proposed new CFF NBS guidelines:** • Use of a floating IRT cutoff over a fixed IRT cutoff • Using a VHIRT referral strategy in CF NBS programs whose variant panel does not include all known pathogenic variants in CFTR2 or does not have a variant panel that achieves at least 95% sensitivity in all ancestral groups within the state

				• CF NBS algorithms should not limit *CFTR* variant detection to the F508del variant or variants included in the ACMG-23 • CF NBS programs screen for all pathogenic *CFTR* variants as identified by CFTR2 • Conducting CFTR variant screening twice weekly, or more frequently as resources allow • Inclusion of a CFTR sequencing tier following IRT and CFTR variant panel testing to improve the specificity and predictive value of CF NBS • Both the primary care provider and CF specialist be notified of abnormal NBS results Dr. Antos led the following discussion (see attached slides): IRT, then do a panel of genes. No limit to variant recommendation on the panel. Change in sequence? Need to decide if switching the algorithm. If do, what is included? How? What to do with carriers? How to report to PCPs (may miss some children going forward)?

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				What are the 3rd Tier changes? Not have to sweat test carriers. Questions – what happens to children who are known carriers? Are they notified? What education is provided? What does the report look like? If identifying carriers, have educational materials set beforehand (parent carrier letter).
11:40-11:50	**Review of Current CF Carrier Fact Sheet & GC List Documenting Educational Resources**	Tami/All	Please review the fact sheet as well as the list of representatives	Tami will send out the current CF Carrier fact sheet with the draft minutes for everyone to review to determine if it should continue to be used and if so, what updates are needed. Also, everyone should share any links to resources used and all will review proposed external links to determine preferred resources to be used. The subcommittee reviewed the current Genetic Counselor state representative list and provided update suggestions. Tami will send out for review and final suggested edits. The subcommittee also reviewed the current subcommittee membership/voting members document and made suggestions for updates needed. Dr. Nancy Bass was suggested to replace Dr. Harmelink for SMA discussions. Dr. Harmelink left his position at MCW. Tami

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				will reach out to Dr. Bass to see if she is interested in joining the subcommittee. Dr. Antos will reach out and invite a parent to join the subcommittee as a parent representative.
11:50	**Plan Next Meeting/Agenda Items**	Dr. Antos/All		Next Meeting Agenda Items: • Revisit possible SWT TAT project • CF National Indicator Report • Review & Confirm Subcommittee membership /voting members • Review NBS guidelines, when finalized

Next meeting date: TBD

"Parking Lot" Items:

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Guideline participants

- CF clinicians
  - Meghan McGarry (co-lead author)
  - Philip Farrell
  - Clement Ren
  - Susanna McColley
- General pediatrics
  - Steven Hicks
- Genetic counselor
  - Karen Raraigh (co-lead author)
- Parents
  - Cambrey White
  - Karey Padding
  - Faith Shropshire
- Librarian
  - Q. Eileen Wafford
- Public health professionals
  - Debra Freedenberg
  - M. Christine Dorley
  - Kathryn Tullis
  - Marci Sontag
- Advisor
  - Jeffrey Brosco (HRSA)
- CFF staff
  - Marissa Taylor
  - Al Faro
  - Runyu Wu
  - Sarah Hempstead
  - Leslie Powell
  - Sarah Webster-Mellon

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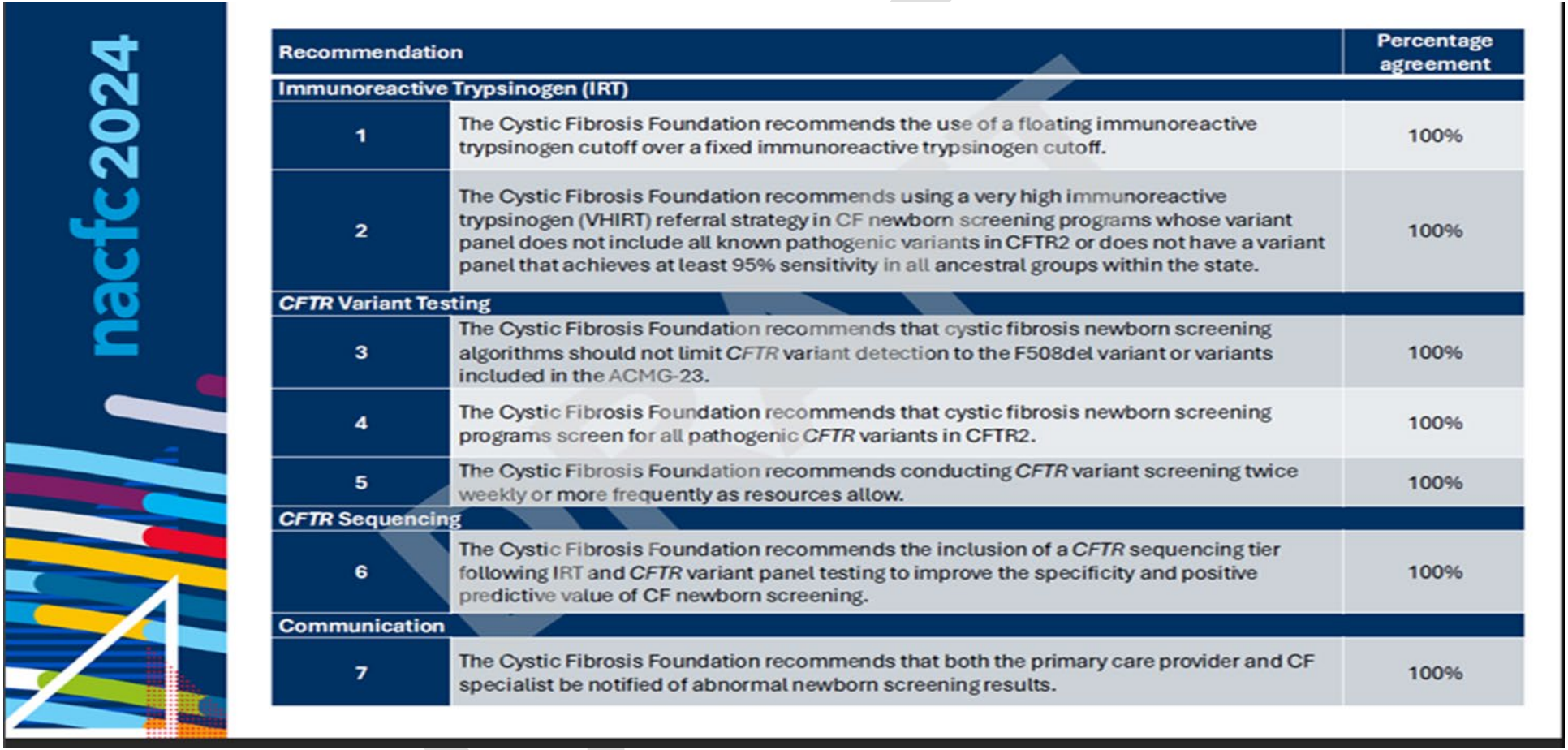

Recommendation		Percentage agreement
Immunoreactive Trypsinogen (IRT)		
1	The Cystic Fibrosis Foundation recommends the use of a floating immunoreactive trypsinogen cutoff over a fixed immunoreactive trypsinogen cutoff.	100%
2	The Cystic Fibrosis Foundation recommends using a very high immunoreactive trypsinogen (VHIRT) referral strategy in CF newborn screening programs whose variant panel does not include all known pathogenic variants in CFTR2 or does not have a variant panel that achieves at least 95% sensitivity in all ancestral groups within the state.	100%
***CFTR* Variant Testing**		
3	The Cystic Fibrosis Foundation recommends that cystic fibrosis newborn screening algorithms should not limit *CFTR* variant detection to the F508del variant or variants included in the ACMG-23.	100%
4	The Cystic Fibrosis Foundation recommends that cystic fibrosis newborn screening programs screen for all pathogenic *CFTR* variants in CFTR2.	100%
5	The Cystic Fibrosis Foundation recommends conducting *CFTR* variant screening twice weekly or more frequently as resources allow.	100%
***CFTR* Sequencing**		
6	The Cystic Fibrosis Foundation recommends the inclusion of a *CFTR* sequencing tier following IRT and *CFTR* variant panel testing to improve the specificity and positive predictive value of CF newborn screening.	100%
Communication		
7	The Cystic Fibrosis Foundation recommends that both the primary care provider and CF specialist be notified of abnormal newborn screening results.	100%

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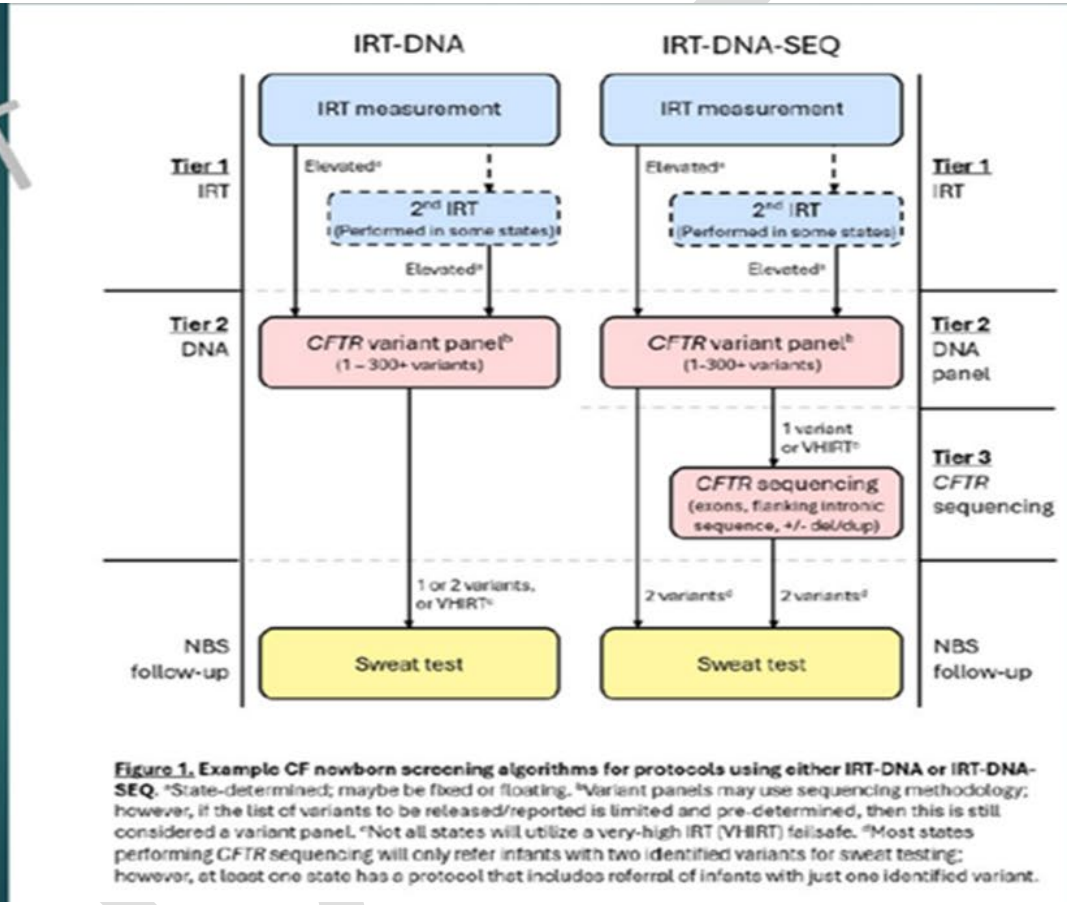

Figure 1. Example CF newborn screening algorithms for protocols using either IRT-DNA or IRT-DNA-SEQ. [a]State-determined; maybe be fixed or floating. [b]Variant panels may use sequencing methodology; however, if the list of variants to be released/reported is limited and pre-determined, then this is still considered a variant panel. [c]Not all states will utilize a very-high IRT (VHIRT) fail-safe. [d]Most states performing *CFTR* sequencing will only refer infants with two identified variants for sweat testing; however, at least one state has a protocol that includes referral of infants with just one identified variant.

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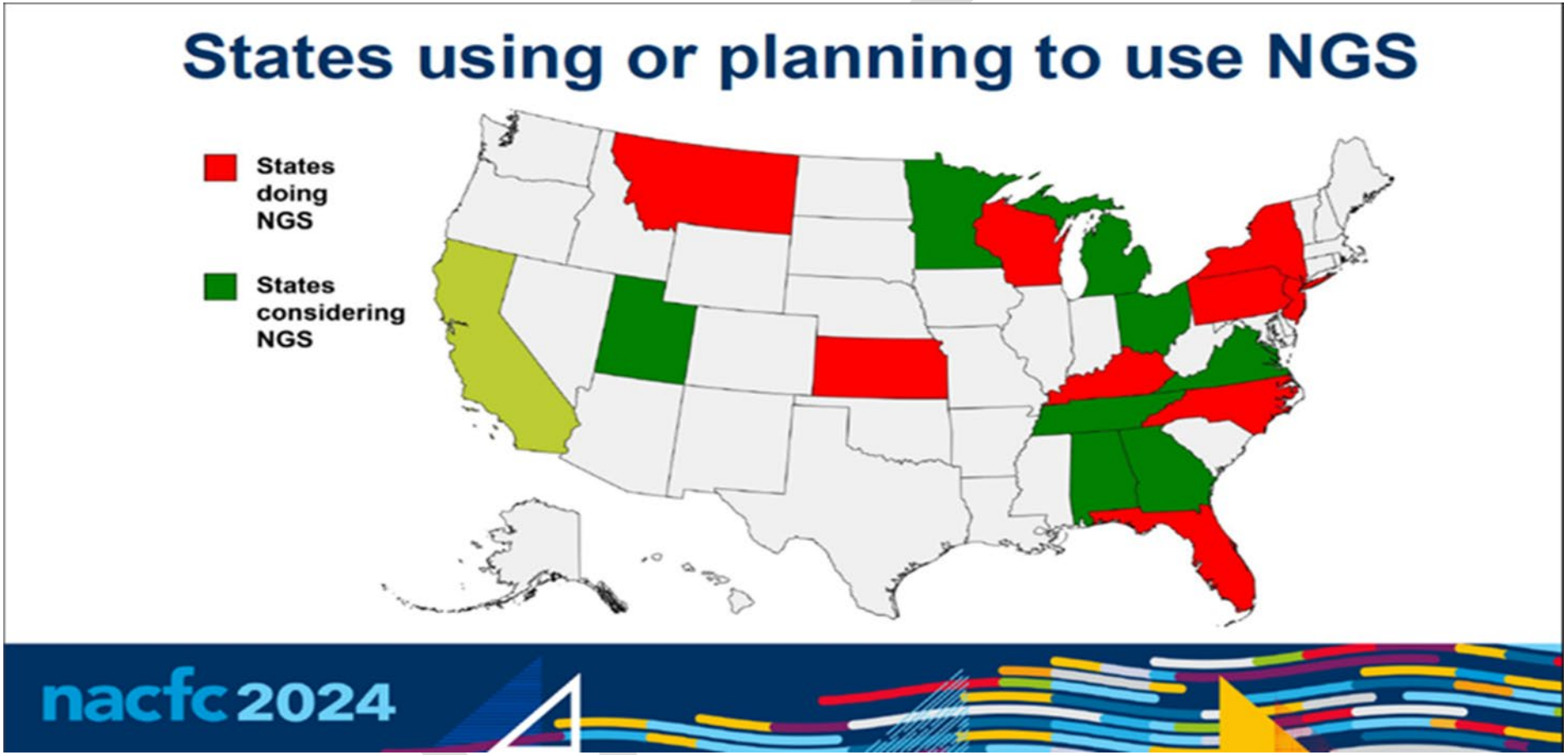

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