(LBSAT255) Real World Performance of the Afirma Genomic Sequencing Classifier (GSC) - A Meta-analysis

Christian E. Nasr, MD,[1] Massimiliano Andrioli, MD, PhD,[2] Mayumi Endo, MD,[3] R Mack Harrell, MD,[4] Masha J. Livhits, MD,[5] Ibitoro Osakwe, MD, MBA,[6] Preethi Polavarapu, MBBS,[7] Shuanzeng Wei, MD, PhD,[8] Xingyu Zheng, PhD,[9*]
Ruochen Jiang, PhD,[9*] Yangyang Hao, PhD,[9*] Jing Huang, PhD,[9*] Joshua P. Klopper, MD,[9*] Richard T. Kloos, MD,[9*] Giulia Kennedy, PhD,[9*] Trevor E. Angell, MD.[10]

1. University of Arizona College of Medicine Phoenix, AZ, USA. 2. EndocrinologiaOggi, Rome, Italy. 3. University of Washington, Seattle, WA, USA. 4. Memorial Health System, Hollywood, FL, USA. 5. UCLA, Los Angeles, CA, USA. 6. Umass Chan Medical School, Baystate, Springfield, MA, USA.
7. University of Nebraska Medical Center, Omaha, NE, USA. 8. Fox Chase Cancer Center, Philadelphia, PA, USA. 9. Veracyte, Inc, South San Francisco, CA, USA. 10. Keck School of Medicine of USC, Los Angeles, CA, USA.
*Potential conflict of interest may exist. Refer to the Meeting App.

BACKGROUND

- The Afirma GSC aids in the clinical decision making for patients with indeterminate thyroid nodule cytology (ITN). The 2018 GSC validation study was based on a cohort of ITN samples collected prospectively from multiple community and academic centers. All patients underwent surgery without known genomic information and were assigned a histopathology diagnosis by an expert panel blinded to all genomic information.
- The results showed (at a 24% cancer prevalence – point estimate and 95% CI):
  - Sensitivity (SN) - 91% (79-98)
  - Specificity (SP) - 68% (60-76)
  - Negative Predictive Value (NPV) - 96% (90-99)
  - Positive Predictive Value (PPV) - 47% (36-58)
- Thirteen independent GSC post-validation studies have been published. This study's objective is to compare the real world (RW) GSC performance to the clinical validation (CV) study metrics.

META-ANALYSIS RULES AND ASSUMPTIONS

- At least one patient with molecular benign results must have surgery for that study to be included in SN, SP and NPV analysis and in these studies, molecular benign results without surgical histology are considered true negatives (TN) (as are the molecular benign results with benign surgical histology).
- Patients with suspicious results that do not have surgery are either excluded from the analysis (generating an observed PPV (oPPV) and observed SP (oSP)) or assumed as histology negatives (i.e. false positives), generating a conservative PPV (cPPV) and conservative SP (cSP).
- NIFTP is considered malignant as surgical resection is required to make the diagnosis.

METHODS

- Babazadeh et al and Wei et al were excluded from SN, SP and NPV analysis.
- Data from all studies were pooled using a random-effects model.
- All analyses were done using R package meta (version 4.18-2).

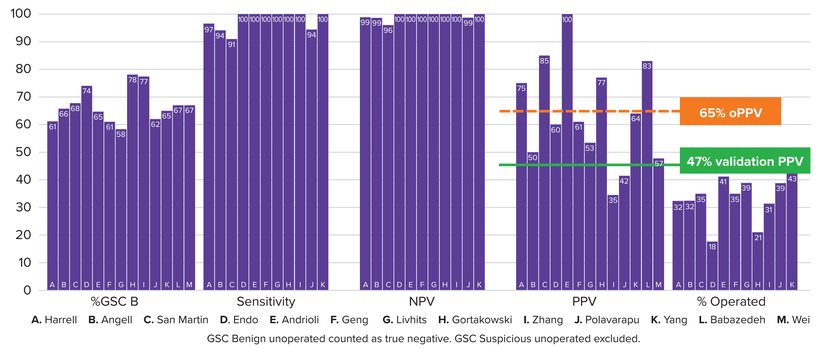
RESULTS

- Figure 1 shows the benign call rate (BCR), SN, NPV, oPPV and % operated where the data is available for each independent, post-validation study.
  - The BCR overall is 67% (65%, 69%).
- In RW studies, the GSC demonstrates (Table 1):
  - SN – 97%
  - NPV – 99%
  - oSP – 88%, cSP – 80%
  - oPPV – 65%, cPPV – 49%
    - Statistically significantly improved over the CV study for oSP, cSP, oPPV, and NPV ($p<0.05$).
- Figures 2 and 3 show the SN and oSP for each included study.
- Figure 4 shows the SN, SP, PPV, NPV and BCR comparing the validation study to the real-world experience (observed – unoperated GSC-S excluded; conservative – unoperated GSC-S considered benign).

DISCUSSION

- RW studies of the Afirma GSC show an improved performance in SP and show a higher ROM in GSC-S nodules than the CV demonstrated (65% vs 47%).
- The RW SP translates to a high benign call rate (as reflected by the RW BCR of 67%), which likely increases the overall rate of clinical observation in lieu of surgery.
- When making the extreme assumption that unoperated GSC-S lesions are all benign, the cPPV matches the CV study (49% vs 47%).
- Possible reasons for this improved performance include:
  - An overrepresentation of Hürthle subtypes in the validation study (20% Hürthle carcinoma (HCC) of malignant histology and 11% Hürthle adenoma of benign histology) relative to RW estimates of HCC prevalence (<7%)[14] along with other histology subtype differences.
  - An enrichment of malignancy in the operated cohort based upon the selection of patients with GSC-S nodules that have surgery (higher clinical risk or more worrisome ultrasound features compared to GSC-S nodules without surgical follow-up).
- In summary, RW GSC data in ITN indicates significantly better performance on several metrics as compared to the validation study, most notably on cSP, oSP and oPPV.

Figure 1 - Afirma GSC Real-World Independent Clinical Utility Studies[1-13]



A. Harrell **B.** Angell **C.** San Martin **D.** Endo **E.** Andrioli **F.** Geng **G.** Livhits **H.** Gortakowski **I.** Zhang **J.** Polavarapu **K.** Yang **L.** Babazedeh **M.** Wei

GSC Benign unoperated counted as true negative. GSC Suspicious unoperated excluded.

Figure 2 - Sensitivity

Study	Events	Total	GSC Proportion	95%–CI
Harrell et al. Endocr Pract 2019	28	29	0.966	[0.822; 0.999]
Angell et al. Thyroid 2019	16	17	0.941	[0.713; 0.999]
Endo et al. Thyroid 2019	15	15	1.000	[0.782; 1.000]
San Martin et al. J Clin Endocrinol Metab 2020	29	32	0.906	[0.750; 0.980]
Andrioli et at. Endocr Pathol 2020	6	6	1.000	[0.541; 1.000]
Geng et al. Cytopathology 2021	22	22	1.000	[0.846; 1.000]
Livhits et al. JAMA Oneal 2021	31	31	1.000	[0.888; 1.000]
Gortakowski et al. Thyroid 2021	10	10	1.000	[0.692; 1.000]
Zhang et al. Diagn Cytopathol 2021	10	10	1.000	[0.692; 1.000]
Polavarapu et al. J Endocr Soc 2022	17	18	0.944	[0.727; 0.999]
Yang et al. J Am Soc Cytopathol 2022	9	9	1.000	[0.664; 1.000]
	199		**0.972**	**[0.917; 0.991]**

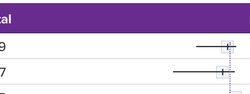


Figure 3 – Observed Specificity

Study	Events	Total	GSC Proportion	95%–CI
Harrell et al. Endocr Pract 2019	84	93	0.903	[0.824; 0.955]
Angell et al. Thyroid 2019	74	90	0.822	[0.727; 0.895]
Endo et al. Thyroid 2019	125	135	0.926	[0.868; 0.964]
San Martin et al. J Clin Endocrinol Metab 2020	79	84	0.940	[0.867; 0.980]
Andrioli et at. Endocr Pathol 2020	11	11	1.000	[0.715; 1 .000]
Geng et al. Cytopathology 2021	81	95	0.853	[0.765; 0.917]
Livhits et al. JAMA Oncol 2021	105	132	0.795	[0.717; 0.861]
Gortakowski et al. Thyroid 2021	57	60	0.950	[0.861; 0.990]
Zhang et al. Diagn Cytopathol 2021	106	125	0.848	[0.773; 0.906]
Polavarapu et al. J Endocr Soc 2022	74	98	0.755	[0.658; 0.836]
Yang et al. J Am Soc Cytopathol 2022	32	37	0.865	[0.712; 0.955]
	960		**0.877**	**[0.832; 0.910]**

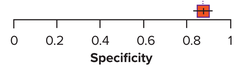
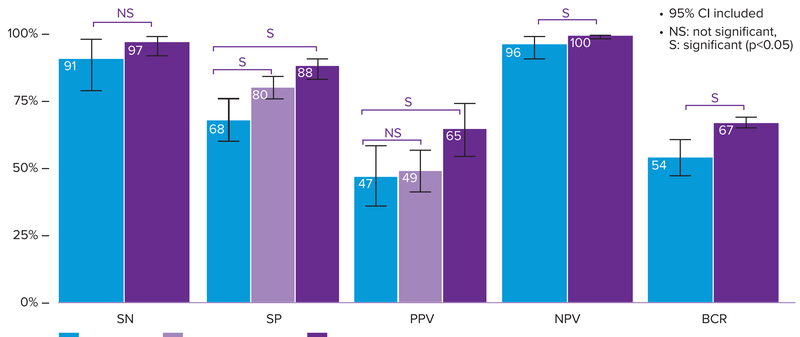


Table 1 – Performance Analysis of the Afirma GSC When Excluding Unoperated GSC-S Lesions or Considering Them Benign (False Positives)

	Validation Study	Meta-analysis Excluding Validation Study *GSC-S unoperated excluded*	Meta-analysis Excluding Validation Study *GSC-S unoperated considered benign*	Post-validation vs CV P-value of Difference *GSC-S unoperated excluded*	Post-validation vs CV P-value of Difference *GSC-S unoperated considered benign*
Sensitivity	0.911 (0.788, 0.975)	0.972 (0.917, 0.991)	0.972 (0.917, 0.991)	0.122	0.122
Specificity	0.683 (0.6, 0.757)	0.877 (0.832, 0.91)	0.804 (0.759, 0.842)	**3.09e-06**	**0.004**
PPV	0.471 (0.363, 0.581)	0.649 (0.544, 0.741)	0.493 (0.413, 0.574)	**0.019**	0.748
NPV	0.961 (0.904, 0.989)	0.995 (0.98, 0.999)	0.995 (0.98, 0.999)	**0.018**	**0.018**

Figure 4 - Performance Comparison: CV vs RW Studies



- 95% CI included
- NS: not significant, S: significant ($p<0.05$)

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