Consultation response - Merlin Assay evaluation by the Danish Health Care Quality Institute

Framework of the evaluation:

Real-world practice data in Denmark highlights the true unmet medical need in T1b patients

- According to nationwide registry data from the Melanoma Database in Denmark, 231 patients in stage T1 received an SLNB in 2024 (T1a = 79, T1b = 155)(1)(Figure 1). This real-world practice data on SLNB procedures indicates a current sizable unmet medical need for metastatic risk assessment in T1b patients (1).
- By using the Merlin Assay, SLNB procedures are avoided in [redacted] of the T1b patients, as estimated in the whole cohort analysis reported in the value dossier submitted part of the evaluation (2). In addition, it was shown in the MERLIN_001 study by Hieken et al. that the use of the Merlin Assay can risk-stratify as High Risk a subset of patients in the T1b group, as their SLN positivity rate increased from 8.7% to 16% (3).
- Adding the T1b population to the current analysis with T2 patients only, would therefore be a better reflection of the real-world practice in Denmark and bring clinical benefits to a broader population that currently has an unmet medical need, while offsetting the associated economic cost for the healthcare system.

Clinical effectiveness and safety:

The Merlin Assay was designed to accurately de-select patients for SLNB, therefore a high sensitivity and low specificity is expected.

- The sensitivity and specificity thresholds defined initially in the evaluation design are not appropriate for a rule-out test. The Merlin Assay was designed to maximize sensitivity and negative predictive value for accurately de-select patients for a surgical procedure that is negative in the majority of patients (70–85%)(4). Therefore, we believe it is an acceptable trade-off to achieve a high negative predictive value and low false-negative rate with a modest reduction in specificity, as is the nature of this rule-out test.
- Current Danish clinical melanoma guidelines recommend SLNB in T2a patients (with a typical SLNB positivity rate of >10%), thus a SNL positivity below 10% is clinically acceptable. Therefore, a negative predictive value of at least 90% should be considered clinically relevant. Additionally, the SLNB carries a 10-20% false-negative rate (4).
- While the high false positivity rate is among the main observations highlighted by the expert committee, a false positive result changes nothing relative to current practice in Denmark among patients considered as High Risk; patients undergo SLNB under existing guideline criteria already. No patient receives a procedure they would not otherwise have had, and the total number of SLNB procedures can only decrease.
- Another important aspect that does not appear to have been considered in the evaluation by the committee is the subgroup of SLNB-eligible patients who are unable to undergo SLNB, do not undergo the procedure, or experience an unsuccessful SLNB. These patients can still be assessed using the Merlin Assay. This is illustrated in the prospective study by Stassen et al. (2023), in which 260 patients were tested with the Merlin Assay, but only 222 had a valid SLNB result. In 20 patients, a successful SLNB could not be performed because the anatomical location made surgery infeasible or because the sentinel lymph node could not be identified through imaging (5).
- We also performed a decision curve analysis for the T2a patient group (Appendix, Figure 2), which demonstrates that the use of the Merlin Assay (CP-GEP; green line) provides a greater net benefit than both a "treat all" strategy (all patients undergo SLNB; red line), and a "treat none" strategy (no patients undergo SLNB; blue line) at threshold probabilities of 10% and higher (i.e., the SLNB

positivity rate in a given population). This means that at a threshold of 8% SLNB positivity rate, the Merlin Assay offers a net clinical benefit compared with the current standard practice of performing SLNB in all patients with T2a melanoma, highlighting its value and clinical relevance of its performance among T2a patients.

- De-selection of true low risk patients for SLNB is still cost saving despite false positives and leads to an improvement of patients' health outcomes. This can be even greater in a broader population (Base-case results: 3.1m kr in savings while achieving additional 4.35 QALYs in the aggregated modelled cohort).

Patient-relevant outcome measures:

In real-world commercial setting SkylineDx delivers Merlin Assay results within 5 working days

- SkylineDx has an extensive experience of delivering a comprehensive laboratory service from its central laboratory to other European countries (such as Germany).
- On average, once a sample is received, processing is done in 3-5 working days. We believe the additional time required to perform the analyses does not significantly increase time for results to be available to inform clinical decision-making, compared to current practice in Denmark.
- Therefore, adoption of the Merlin Assay will not require major additional costs to the health care system for local delivery within Denmark.
- Unlike the previously reported study in the Netherlands, in a real-world commercial setting SkylineDx delivers Merlin Assay result report with a turnaround time within 5 days.

SLNB-related complications

Despite low frequency of complications, the duration and cost impact is potentially high.

- The clinical impact of SLNB-related complications after a full node resection, such as lymphedema and nerve damage, is likely to result in long-lasting detrimental impact on patients' quality of life, while being of relatively low frequency. This impact adds potentially high costs for the health care system. In addition, forgoing a procedure requiring general anesthesia reduces the risk of potential complications as well as associated psychological distress.
- Avoiding long-term complications of SLNB by the adoption of the Merlin Assay therefore create economic savings to the Danish healthcare system, since these events do require long-term monitoring and healthcare resource use.

Health economic evaluation:

For fair health economic evaluation of the Merlin Assay, the full treatment pathway has to be incorporated

- Excluding costs of immunotherapy in the cost-effectiveness analysis do not reflect the long-term impact of testing in the clinical pathway of Melanoma patients in Denmark. Its inclusion also aligns with the evaluation framework in which prognosis of patients was considered.
- The cost-effectiveness analysis includes immunotherapy costs as per clinical guidelines. Stage IIIA patients were assumed to be 25% of all stage III patients as indicated by experts in Denmark. These patients effectively are not considered eligible for treatment in our modelling.
- The developed health economic analysis considered QALYs as a relevant outcome measure to capture the value of the Merlin Assay on the SLNB-related complications and their impact on quality of life.
- A fair assessment of the economic value of the Merlin Assay has to incorporate the appropriate population categories (i.e., T1b in addition to T2) and include treatment costs to define a price setting that captures its value to the Danish health care system.

Appendix

Figure 1. Patients undergoing sentinel lymph node biopsy with a positive sentinel lymph node, by T category, 2023 and 2024 in Denmark

Patologisk T-kategori	Patienter med invasive tumorer 2024		Patienter med sentinel lymfeknude biopsi 2024		Patienter med positiv sentinel node 2024		Patienter med invasive tumorer 2023		Patienter med sentinel lymfeknude biopsi 2023		Patienter med positiv sentinel node 2023	
	Antal	%	Antal	%	Antal	%	Antal	%	Antal	%	Antal	%
T1, i alt	**1797**	**(100,0)**	**235**	**(13,1)**	**5**	**(2,1)**	**1879**	**(100,0)**	**294**	**(15,6)**	**11**	**(3,7)**
T1 Uspecificeret eller ukendt	5	(100,0)	#	(#)	0	(0,0)	#	(#)	#	(#)	0	(0,0)
T1a	1351	(100,0)	79	(5,8)	#	(#)	1403	(100,0)	119	(8,5)	#	(#)
T1b	441	(100,0)	155	(35,1)	4	(2,6)	475	(100,0)	174	(36,6)	9	(5,2)
T2, i alt	**574**	**(100,0)**	**510**	**(88,9)**	**58**	**(11,4)**	**572**	**(100,0)**	**510**	**(89,2)**	**55**	**(10,8)**
T2 Uspecificeret eller ukendt	#	(#)	#	(#)	#	(#)	3	(100,0)	#	(#)	0	(0,0)
T2a	513	(100,0)	455	(88,7)	49	(10,8)	516	(100,0)	468	(90,7)	46	(9,8)
T2b	60	(100,0)	54	(90,0)	8	(14,8)	53	(100,0)	41	(77,4)	9	(22,0)
T3, i alt	**343**	**(100,0)**	**274**	**(79,9)**	**65**	**(23,7)**	**307**	**(100,0)**	**255**	**(83,1)**	**64**	**(25,1)**
T3 Uspecificeret eller ukendt	7	(100,0)	7	(100,0)	#	(#)	0	(100,0)	#	(#)	0	(0,0)
T3a	209	(100,0)	167	(79,9)	36	(21,6)	186	(100,0)	161	(86,6)	38	(23,6)
T3b	127	(100,0)	100	(78,7)	27	(27,0)	121	(100,0)	93	(76,9)	26	(28,0)
T4, i alt	**237**	**(100,0)**	**129**	**(54,4)**	**31**	**(24,0)**	**186**	**(100,0)**	**123**	**(66,1)**	**31**	**(25,2)**
T4 Uspecificeret eller ukendt	#	(#)	#	(#)	0	(0,0)	#	(#)	#	(#)	0	(0,0)
T4a	84	(100,0)	56	(66,7)	11	(19,6)	55	(100,0)	42	(76,4)	7	(16,7)
T4b	152	(100,0)	72	(47,4)	20	(27,8)	130	(100,0)	80	(61,5)	24	(30,0)
Uklassificeret	96	(100,0)	57	(59,4)	5	(8,8)	119	(100,0)	85	(71,4)	9	(10,6)
I alt	3047	(100,0)	1205	(39,5)	164	(13,6)	3063	(100,0)	1267	(41,4)	170	(13,4)

[redacted]



[redacted]

References

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