Submitted by:
Dharminder Chahal, CEO
SkylineDx, B.V.
16 Marconistraat, Rotterdam, the Netherlands
Phone: +31107038410
Email: d.chahal@skylinedx.com
Date of request: April 18, 2018
NCCN Guidelines Panel: Multiple Myeloma

On behalf of SkylineDx, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data for inclusion of the SKY92 high risk signature (MMprofiler) in the prognostic evaluation of multiple myeloma patients.

Specific Change: Recommend the SKY92 high risk signature as a routine component of the prognostic evaluation of newly diagnosed and relapsed refractory multiple myeloma.

Current NCCN Guidelines Version 4.2018 Multiple Myeloma:
*The NCCN Panel unanimously agreed that although **GEP** is not currently routinely used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.*

Proposed:
*The NCCN Panel unanimously agreed that **GEP** is a useful tool and may be helpful in NDMM and RRMM patients to estimate the aggressiveness of the disease and individualize treatment.*
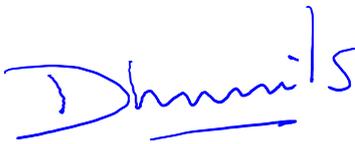
FDA Status: FDA clearance is not required for this test, as it is performed in the central laboratory of SkylineDx that is regulated under the Clinical Laboratory Improvement Amendments (CLIA).

Rationale: SKY92 is available for clinical use in the US. SKY92 is a significant prognostic marker in all currently analyzed NDMM and RRMM datasets tested [1-5]. We recently added significant SKY92 data in elderly patients [4]. Mayo Clinic mSMART guidelines acknowledge treatment decisions based on high risk GEP. There are currently two ongoing risk stratified trials that use SKY92 (MUKnine and SWOG S1211). Furthermore, we now have real world experience from our central laboratory in Europe, serving MM patients case by case.

SKY92 high risk GEP signature is specific and robust for predicting outcome in MM. The following results confirm this. **1.** Kuiper R. et al have shown in a combined dataset of 4750 cases that the combination of ISS plus SKY92, has the **best performance** for detecting high risk as well as low risk multiple myeloma [1]. **2.** SKY92 has been **clinically validated** in 8 cohorts (total n=1390 cases including various PI and IMiD therapies) resulting in an average HR 3.75 (range 2.4 - 10.3). **3.** The signature is **available in the US** for clinical use (CLIA/LDT). **4.** All SKY92 software was developed according clinical standards, is fully **automated and secure**. **5. Turnaround time** of real world patient data in our European central laboratory is 9.2 days. **6.** Risk stratification by SKY92+ISS achieved **independent prognostic value** in a multivariate model with FISH markers t(4;14) and del(17p) in multiple myeloma [2]. **7.** SKY92 is an **independent prognostic marker** in a multivariate model with FISH (t(4;14) and/or del(17p)) in both HOVON65 (n=230) as in MRC-IX (n=169) cases [3]. **8.** SKY92 has been validated in **elderly** patients of the HOVON-87/NMSG-18 study and **outperforms R-ISS** [4]. **9.** SKY92 was **superior** over other GEP signatures and demonstrated in this MMRF/MMGI cohort that it identified the largest proportion of high risk patients with the largest hazard ratio [5].

Sincerely,

Dharminder Chahal, CEO

References

1. Kuiper R et al, Blood. 2015 Oct 22;126(17):1996-2004
2. Van Vliet M.H. et al. EHA 2016 - P283
3. Van Beers E.H. et al. EHA 2015 Haematologica 2015, EHA Abstract P661
4. Kuiper R. et al. EHA 2017, abstract P677
5. van Beers E.H. et al. Clin Lymphoma Myeloma Leuk. 2017 Sep;17(9):555-562