Public Health System Impact Assessment: Factsheet for MPS-1 Screening

Condition	MPS-1
Description	Autosomal recessive Lysosomal Storage Disorder caused by a deficiency of alpha-L-iduronidase enzyme; many systems can be affected, including cardiac, respiratory, brain & CNS, and muscle and skeletal; the disease has three phenotypes, which include Hurler (severe form), Hurler/Scheie and Scheie (attenuated forms); current treatments for the disorder include hematopoietic stem cell transplantation (HSCT) for the severe form only and enzyme replacement therapy (ERT)
Expected Incidence	Clinical detection= ~0.54 to 1.15 per 100,000 births (all forms) Detection by laboratory screening= ~1 to ~3 per 100,000 births (all forms); estimates from Missouri pilot Clinically ~61% of all cases are severe, while ~39% are attenuated[1]

Screening Methods		
Measurement Method[2]	*Flow injection tandem mass spectrometry (PE-FIA MS/MS 2014)*	*Fluorometry by digital microfluidics platform*
Data Source(s)	Anonymous research study in collaboration with Drs. Ron Scott and Michael Gelb, and Washington NBS program	Missouri statewide newborn screening pilot with linked specimens and clinical follow-up
Screening Marker	Enzyme Activity	Enzyme Activity
Screening Strategy	Tagged synthetic substrate and measurement by tandem MS/MS	Four MU tagged synthetic substrate and measurement by fluorescence

Resources and Materials		
Minimum Instrumentation, Equipment and Requirements Necessary to Process 50,000 Specimens Annually (Includes Conventional Redundancies)	• Shaker/incubator • Multichannel pipettor • 2 MS/MS (**Note:** MS/MS cannot be multiplexed with amino acids and acylcarnitines) • Nitrogen and exhaust • Plate centrifuge • Solvent/dryer	• Shaker • Multichannel pipettor • 4 digital microfluidics analyzers
Instrumentation Per Detection Workstation to Process 50,000 Annually	1 MS/MS	4 digital microfluidics analyzers
Equipment Suppliers and Availability of Kits, Reagents and Consumables	**MSMS** Perkin Elmer **Artificial Substrates (ASR):** Genzyme is the sole source, distributes through CDC; continued availability of these ASR substrates is unlikely. **Note:** Perkin Elmer (PE) and the University Washington have developed a 6-plex kit, pending FDA approval ~2016 **Consumables:** Routine purchase	**Digital Microfluidics** Baebies (formerly Advanced Liquid Logic, acquired by Illumina, Inc.) is the sole source for DMF instrument **Artificial Substrates:** Baebies is sole source **Consumables:** Baebies is sole source for purchase of microfluidics cartridges

Public Health System Impact Assessment: Factsheet for MPS-1 Screening

Workstation Resources and Capacity		
Specimens (with Controls) Processed at One Workstation	80 to 96 specimens per plate x 1 plate per instrument x 1 instrument = 80 to 96 specimens	40 specimens per plate x 1 plates per instrument x 4 instruments per workstation = 160 specimens
Tech Time to Prepare Specimens (Extraction and Loading Cartridges)	Not available	1 hr.
Instrument Time	3 hrs. MS/MS (multiplexible) to get 1 plate	4 hrs. (multiplex 4 LSDs) to get daily results
Enzyme Incubation Time	16 hrs.	The enzyme incubation occurs very quickly within the cartridge on the platform during the instrument run time
Maximum Number of Specimens to Be Analyzed at One Workstation During An 8 Hour Shift	192 specimens	320 specimens
Space Requirements (Supporting Equipment Not Included)	23 x 32", 14 cu ft. (one MS/MS)	32 x 96" (fluorometry workstation)

Personnel Requirements		
FTE Needed to Process 50,000 Specimens Annually (From Sample Receiving Through Result Interpretation)	1 FTE (one MS/MS)	0.75 FTE
FTE Needed to Process 100,000 Specimens Annually	Not available	Not available

Other Considerations		
LIMs Adjustments	Not available	Not available
Training	Not available	Not available

QC and Reported Screening Results		
Availability of Quality-Control Specimens	In development at CDC, but not yet validated	Proficiency testing materials in development at CDC but not yet validated (developed for Pompe); Routine plate controls and calibrators provided by Baebies
Reported Rate of Retests (Same Specimen)	Not available	~1% of total DBS specimens received will need to be re-punched and re-tested in duplicate due to a breach of the in-house cutoff
Reported Rate of Repeats (Independent Specimen)	Not available	~ 0.49% of specimens will require a repeat/independent specimen to be collected
Rate of Referrals[3]	**Projected rate**= 9/106,526 or ~8 per 100,000	**Reported rate**= 57/117,000 or ~45 per 100,000

Public Health System Impact Assessment: Factsheet for MPS-1 Screening

QC and Reported Screening Results		
Reported Outcomes[3]	#**by type(s):** (n=106,526 DBS) Confirmed= 3 Pseudo def= 0 Carriers= 1 False positives= 3 Poor punch= 2	#**by type(s):** (n=117,000 DBS) Confirmed= 1 Pseudo def= 24 Carriers=3 False positives= 24 Pending= 4 Lost to FU= 1

Estimated $$ Costs[4]		
Equipment Cost (Overhead)	**Equipment purchase for use with reagents:** $220,000-$250,000 for one 1 MS assuming useful life of 10 years, straight-line depreciation of $220-225,000 per year; annual cost of maintenance contract and electricity of $33,200; instrumentation cost per specimen	Not available
Estimated Cost to Laboratory of Reagents or FDA-Approved Kit	Stated costs to manufacture reagents range from ~$0.07-$.10 per specimen for each of the 6 LSDs; $0.42-$0.60 for 6 LSDs ~$0.12-0.15 per specimen for each of the 6 LSDs; ~$0.73-$0.88 for all (assumes 80,000 annual specimens, one-screen state, and one MS/MS)[5] Likely price to be charged by manufacturer will be no less than $1.00 per condition per specimen[6]	Not available
Estimated Reagent Rental Cost (Includes Instruments, Reagents, Cartridges, Service and Tech Support)	Not available	Price charged by manufacturer likely to be no less than $1.00 per condition per specimen
Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)[6]	Level: Advanced Chemist Number: 2 $150,000 for 2 advanced chemist FTEs (salary, benefits overhead)	Level: Junior Chemist Number: 0.75 Assuming $100,000 for 1 Junior Chemist FTE (salary, benefits, overhead)
Estimated Diagnostic Assay Cost	$200-$600	$200-$600
Estimated Diagnostic Molecular Testing Costs	$1000-$2800 (full gene)	$1000-$2800 (full gene)

Short-Term Follow-Up	
Description	Approximately 10-20% FTE from follow-up staff is needed to make staff calls; Diagnostic centers handle positive specimens by conducting Iduronidase (IDUA) enzyme activity assay, urine glycosaminoglycan (GAGs), and genotyping; a geneticist interprets results (Missouri experience)

Public Health System Impact Assessment: Factsheet for MPS-1 Screening

Short-Term Follow-Up	
Case Definition Applicable to Neonatal Period	Iduronidase activity in leukocytes or in culture skin fibroblast must be <1% normal activity
Diagnostic Method & Criteria	Definitive MPS I= IDUA enzyme activity < 1% normal Supportive of diagnosis= Increased GAG levels in urine Genotyping can assist if a known pathogenic mutation is detected
Availability of Diagnostic Centers	There are ~4-5 diagnostic laboratories in the U.S.; Missouri utilizes Greenwood Genetics and Mayo Clinic to conduct genotyping; Missouri utilizes Greenwood Genetics, Mayo Clinic and UPenn for IDUA enzyme level diagnostics

Current Treatment(s)	MPS I – Severe	MPS I – Attenuated
Description and Current Treatment Guidelines with Clinical Identification	**HSCT**= Recommended for patients 2 to 2.5 years with little cognitive decline (≤70 developmental quotient) **ERT** may be given in conjunction with HSCT (pre- and post-HSCT)	**ERT** = standard recommended treatment with current clinical identification
Specialty Providers or Centers	Availability of specialty providers and centers varies by state; each center usually has a defined region it serves; some patients may have to travel long distances to reach a treatment center; this could have major implications on patients who need ERT infusions every two weeks	

[1]Beck M. et al., 2014. The natural history of MPS I: Global perspectives from the MPS I Registry. *Genetics in Medicine*, 16, 759-765.

[2]Other methods not depicted here include LC-MS/MS and fluorometry on microtiter plate.

[3]Caution is needed when comparing number of referrals for these methods. Data from WA specimens entailed retrospective, blinded specimens with no follow-up. Confirmation was by DNA testing. Missouri data was from a prospective population based pilot study with confirmatory testing, diagnosis and follow-up. Screening in Missouri began purposefully conservative to give the highest sensitivity before working to enhance specificity. Missouri's referral rate is expected to decrease once statewide screening is initiated.

[4]Cost estimates presented in this document have a high level of uncertainty at this point in time; the only high throughput clinical laboratory is running digital microfluidics.

[5]Costs for instrumentation and maintenance will vary based on number of annual specimens screened; for example, it will double for states that screen 45,000 specimens vs. 90,000.

[6]FDA kits are pending approval and costs are still unknown.

[7]Personnel costs will vary based on FTE for particular state and number of annual specimens.