Interpreting MORL Complement-Mediated Kidney Disease Genetic and Functional Results

GENETIC TESTING		
Gene	**Chromosomal Location**	**Interpretation**
Complement gene that has been reported to be associated with TMAs/C3G	The specific location on a chromosome of a given gene	**Pathogenic known**: a variant that has been proven to be disease-causing **Likely pathogenic**: a variant that is likely to be disease causing based on current data **Unknown significance:** a variant for which further interpretation is not possible based on available data **Likely benign:** a variant not known to cause disease

PATHWAYS			AUTOANTIBODIES					
CH50 (41-95 Units/mL	**APFA** (50-130%)	**C3b Deposition Assay** (normal)	**FH Autoantibody** (<200 AU)	**FB Autoantibody** (<200 AU)	**Fluid Phase Activity -IFE** (<7.5%)	**C3Nef - C3CSA** (<20%)	**C5Nef- C3CSAP** (<20%)	**C4Nef** (<20%)
Determines whether the CP is overactive or whether a CP protein has been abnormally consumed	Determines whether the AP is overactive or whether an AP protein has been abnormally consumed	Identifies whether abnormal C3 activation is occurring	An antibody that binds to Factor H (FH); can interfere with FH function and compromise AP regulation	An antibody that binds to Factor B (FB); can interfere with C3 convertase regulation; often seen in PIGN	Determines if a protein in the blood is causing complement dysregulation/activation	Antibodies to C3- or C5-convertase, preventing them from naturally falling apart		Similar to C3- or C5-nephritic factors, however they stabilize the classical pathway convertase

BIOMARKERS												
	C3 level (90-180 mg/dL)	**C3c Level** (<1.5 mg/L)	**C4 Level** (15-47 mg/dL)	**FB Level** (22-50 mg/dL)	**Ba Level** (<1.2 mg/L)	**Bb Level** (<2.2 mg/L)	**FD Level** (0.78-1.59 mg/L)	**C5 Level** (13.5-27 mg/L)	**Properdin Level** (10-33 mg/L)	**Soluble C5b-9** (<0.3 mg/L)	**FI Level** (18-44 mg/L)	**FH Level** (180-420 mg/L)
High Result	Represents inflammation or obesity	A breakdown product of C3, suggests overactivity of the AP	Represents inflammation	Represents inflammation	Cleavage products of FB; high levels mean that FB is being consumed excessively; high levels of Ba are also seen with ESKD		High levels of Factor D (FD) suggest declining kidney function irrespective of complement activity	Elevated with terminal complement pathway inhibitor		Increased activity of the terminal complement pathway	Represents inflammation	Represents inflammation
Low Result	Deficient because of a gene abnormality or inappropriately consumed		Deficient because of a gene abnormality or inappropriately consumed	Deficient because of a gene abnormality or consumed due to overactive AP				Suggests terminal pathway hyperactivity	Suggests terminal pathway hyperactivity	Low if on terminal complement blockade	Deficiency typically reflects a gene abnormality	Deficiency typically reflects a gene abnormality or inappropriate consumption

* AP = Alternate Pathway; CP = Classical Pathway; Nef = Nephritic Factor, ESKD= End Stage Kidney Disease; laboratory results may be significantly altered by inappropriate specimen handling; due to the extreme complexity of the complement cascade, assessing complement activity and regulation is best performed by pathway analysis, together with autoantibody testing and biomarker profiling as opposed to doing tests in isolation