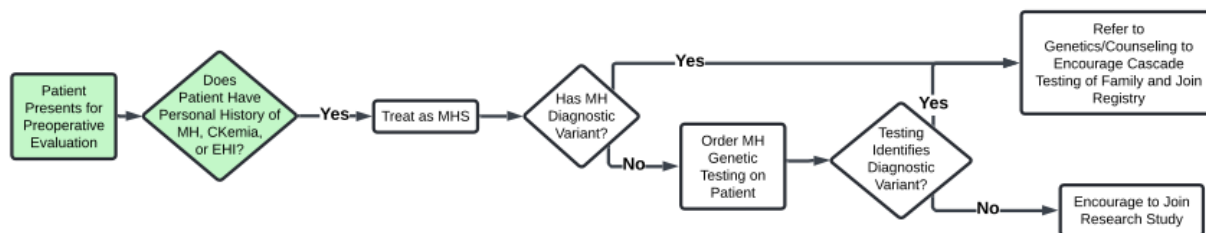


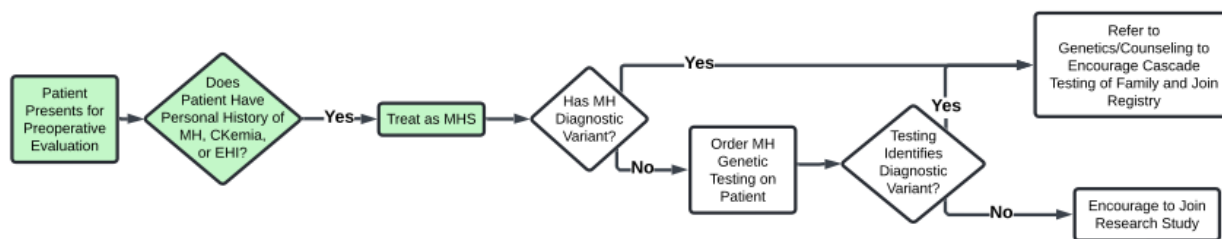
Hypothetical Scenarios

This supplement includes four commonly anticipated (but hypothetical) scenarios to allow the user to gain familiarity and comfort with the use of the flow diagram for management of a patient when performing a preoperative evaluation for an elective surgery in a setting where the default anesthetic management would include a triggering agent (most commonly an inhaled anesthetic). Note that the logical structure has not been altered in any way compared to the flow diagram in Figure 1 in the main manuscript. We have only pruned and compacted it for clarity and easy of use.

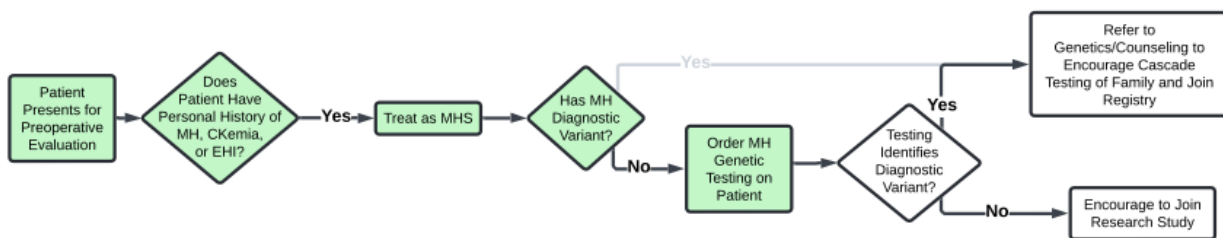
Scenario 1 A 53-year-old man presents for a preoperative evaluation for colectomy and ostomy placement. In the evaluation, he reports a prior surgery with an immediate postoperative reaction including severe fever and muscle spasm. His prior anesthetic record shows use of Sevoflurane anesthetic and rocuronium paralysis, and that he had generalized muscular rigidity, hyperthermia, respiratory acidosis on blood gas, and cola-colored urine. He recalls that a doctor told him he should get genetic testing done but he never got around to it. The anesthesiologist diagnoses him (clinically) as being Malignant Hyperthermia Susceptible and plans the case accordingly using total intravenous anesthetic and discusses the plan with the patient and his surgical colleague.



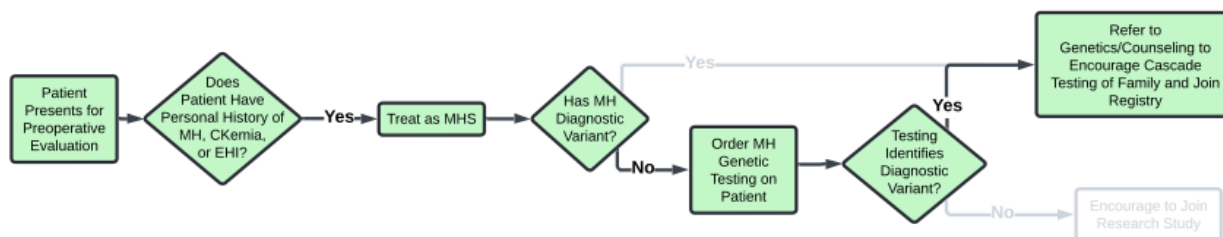
The history and medical records are more than sufficient to diagnose this patient as MH susceptible and he should only be anesthetized with non-triggering agents for the rest of his life. No genetic test result should change that clinical diagnosis nor should it alter that management plan. However, a genetic test result can be extremely useful for his family members, so the anesthesiologist should continue to follow the flow diagram.



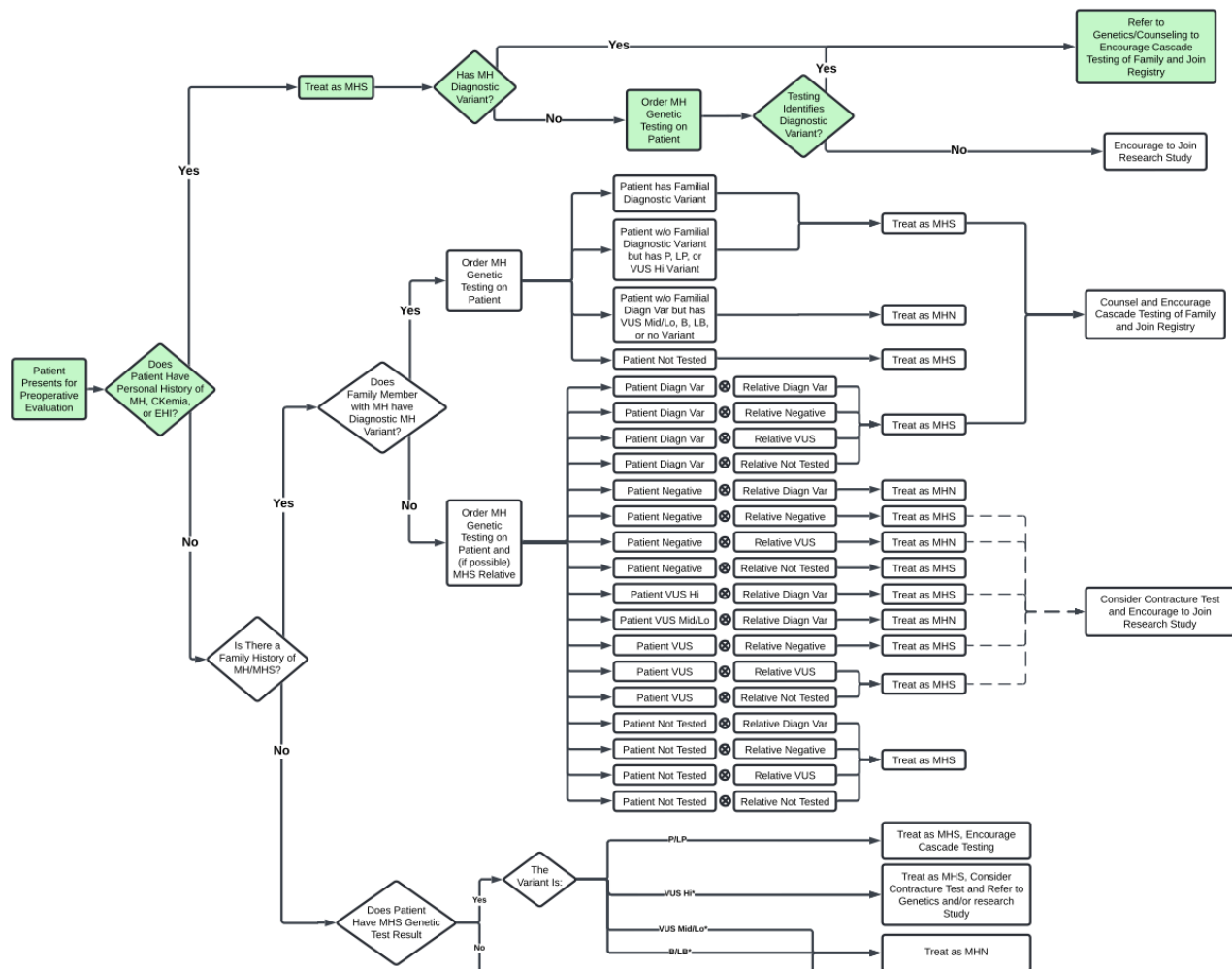
According to the history and the chart, no genetic testing has been performed on this man, so the anesthesiologist orders a three gene (*RYR1*, *CACNA1S*, and *STAC3*) full sequencing MHS gene testing panel on him.



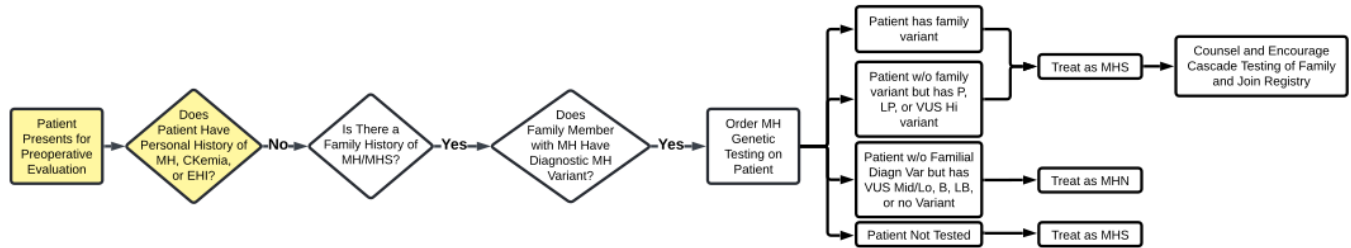
Several weeks after the successful surgery, the anesthesiologist is alerted to the return of a genetic test result for a known variant in *RYR1*, that is pathogenic for *RYR1*-related malignant hyperthermia susceptibility. The anesthesiologist follows up with the patient by referring him to genetics for familial cascade testing, advising him in the strongest possible terms that doing so could be life saving for his family members.



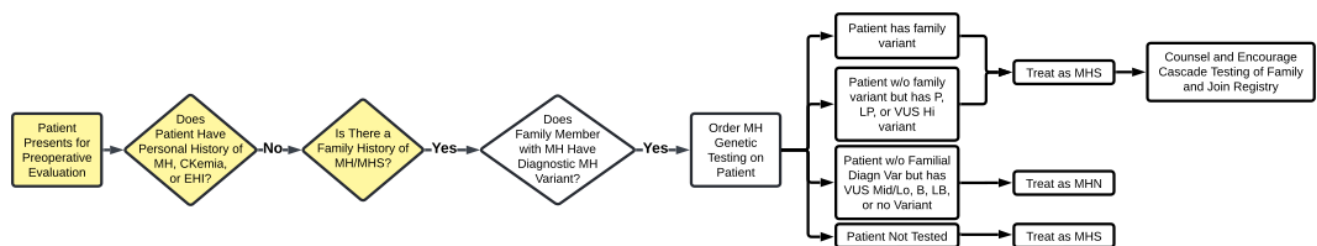
Shown below is Scenario 1, shown in the context of the full flow diagram:



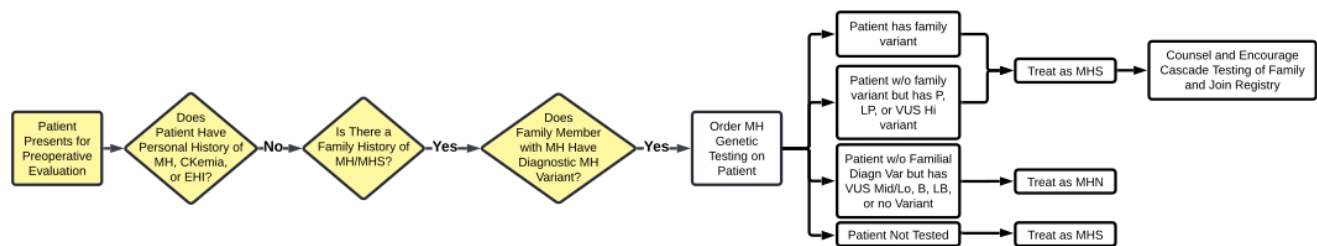
Scenario 2. A 69-year-old woman presented for preoperative evaluation for hysterectomy for multiple leiomyomas. She has no personal history of untoward reactions to anesthesia.



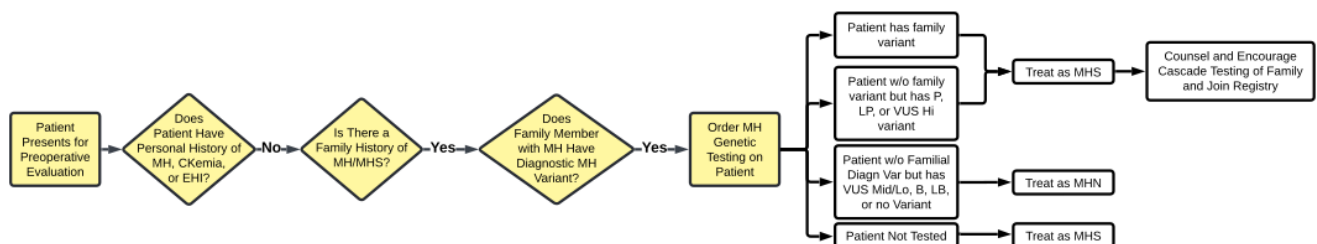
From the family history, she reports that that her daughter had an apparent MH reaction for an emergency cesarean delivery.



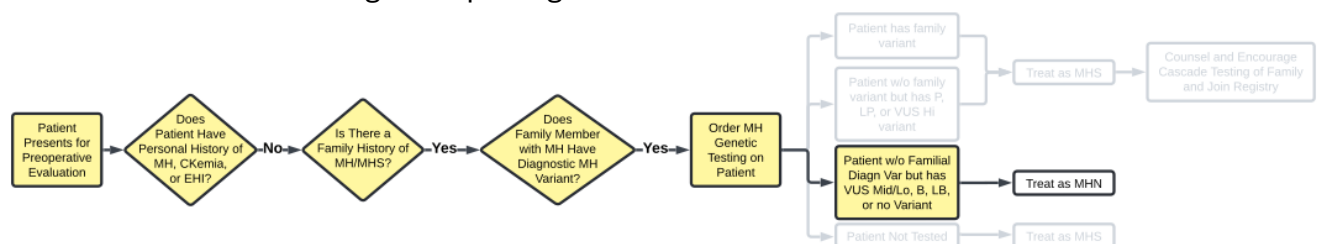
The daughter had genetic testing and was found to have a pathogenic variant in *RYR1*.



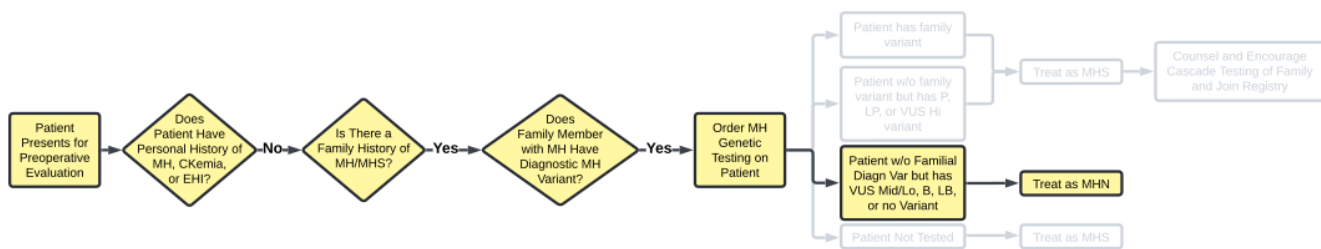
The anesthesiologist orders a three gene (*RYR1*, *CACNA1S*, and *STAC3*) full sequencing MHS gene testing panel on the preoperative evaluation patient (mother).



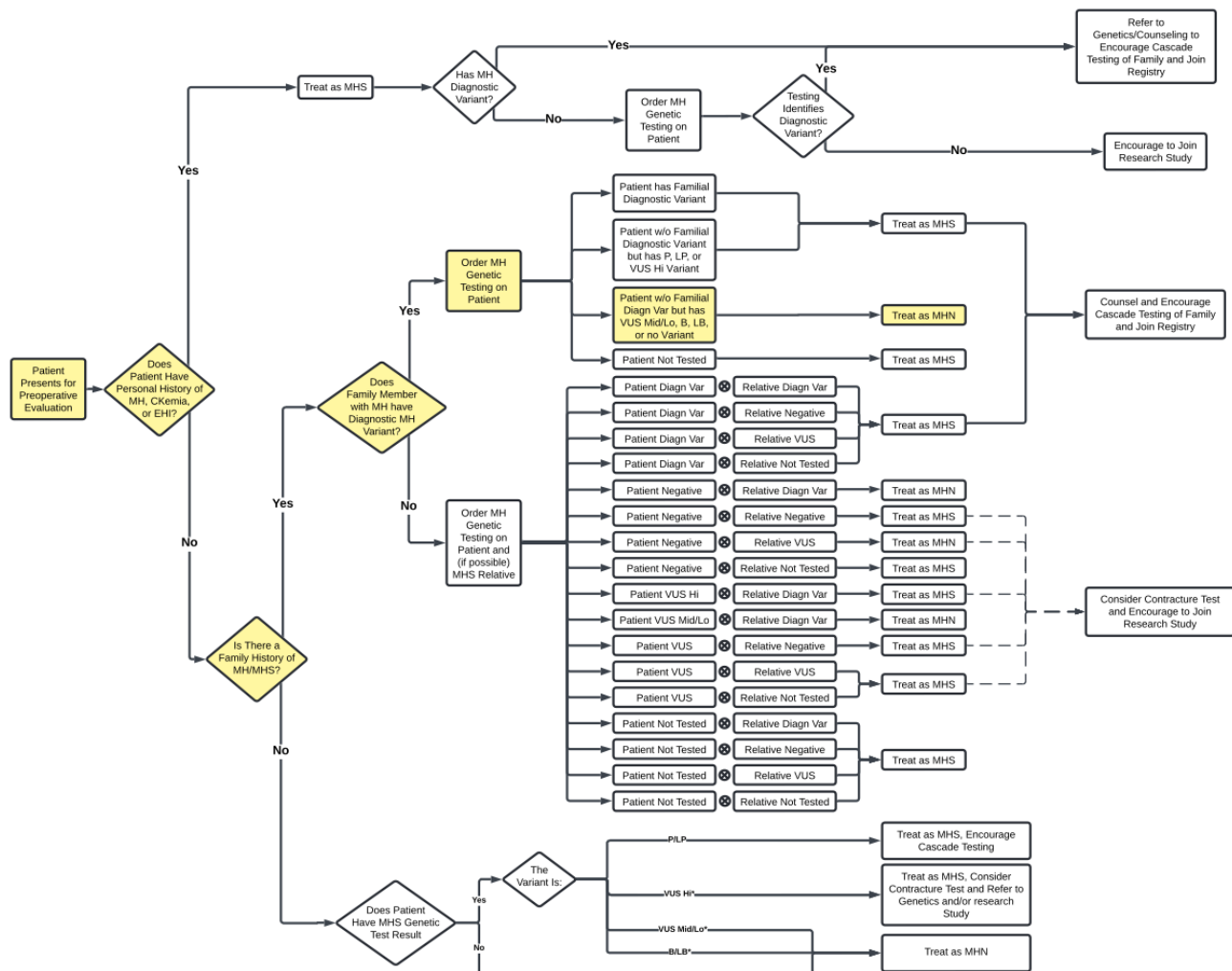
The mother's result is returned, and she was found to only have a single likely benign variant in *RYR1* and does not have her daughter's pathogenic variant.



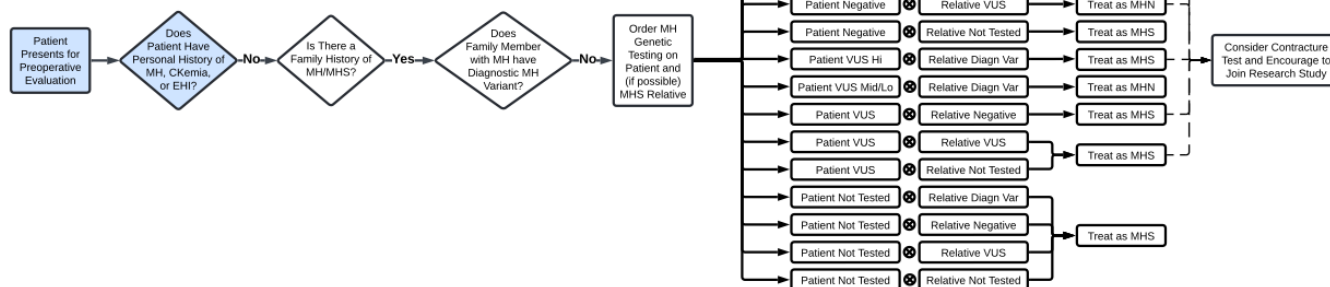
Based on the mother's test result, the anesthesiologist elects to perform the case using their standard clinical recommendation of inhaled anesthetic.



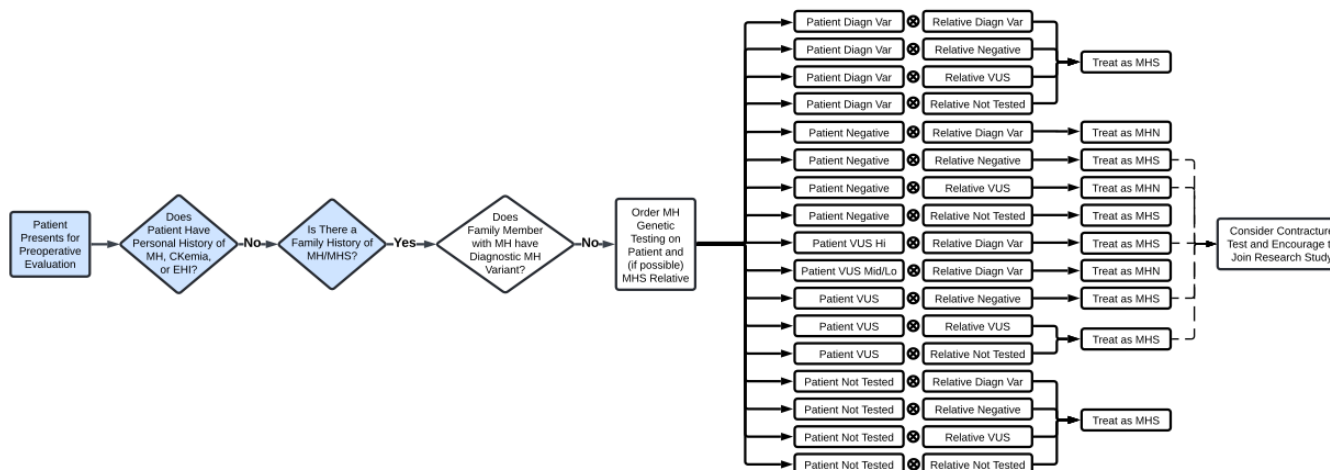
Shown below is Scenario 3 shown in the context of the full flow diagram:



Scenario 3. An 8-year-old boy presents for preoperative evaluation for orthopedic surgery for a leg length discrepancy. He has not previously had surgery or general anesthetic and thus no untoward anesthesia reaction history.



He has a 14-year-old sister who had an apparent MH reaction with fever, rigidity, acidosis, and hyperCKemia during a procedure for placement of a ventriculoperitoneal shunt.

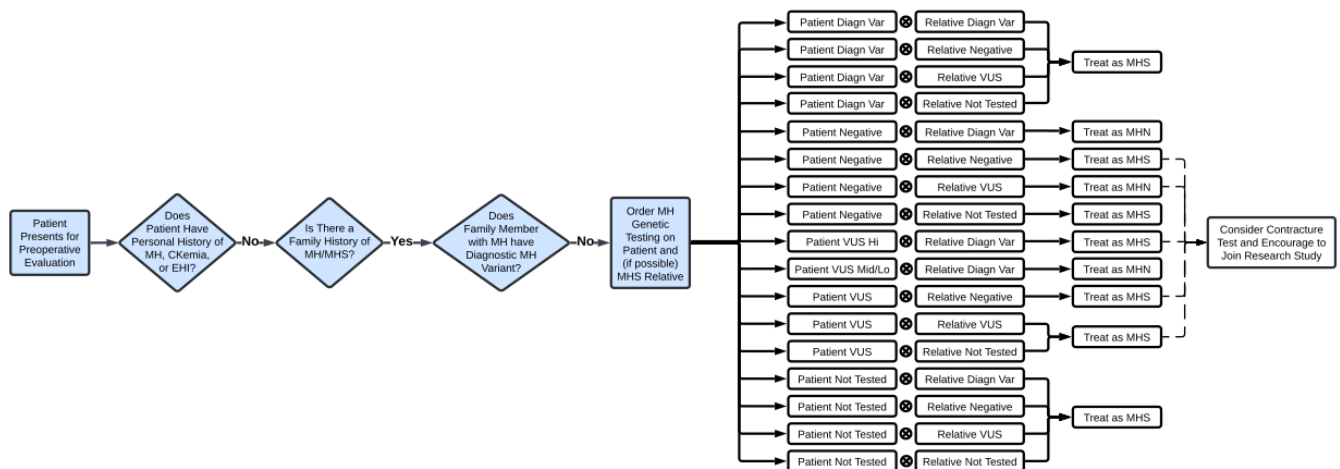


Because of her other health problems (epilepsy and intellectual disability), the family has not had the time nor energy to get her genetically tested for MHS.

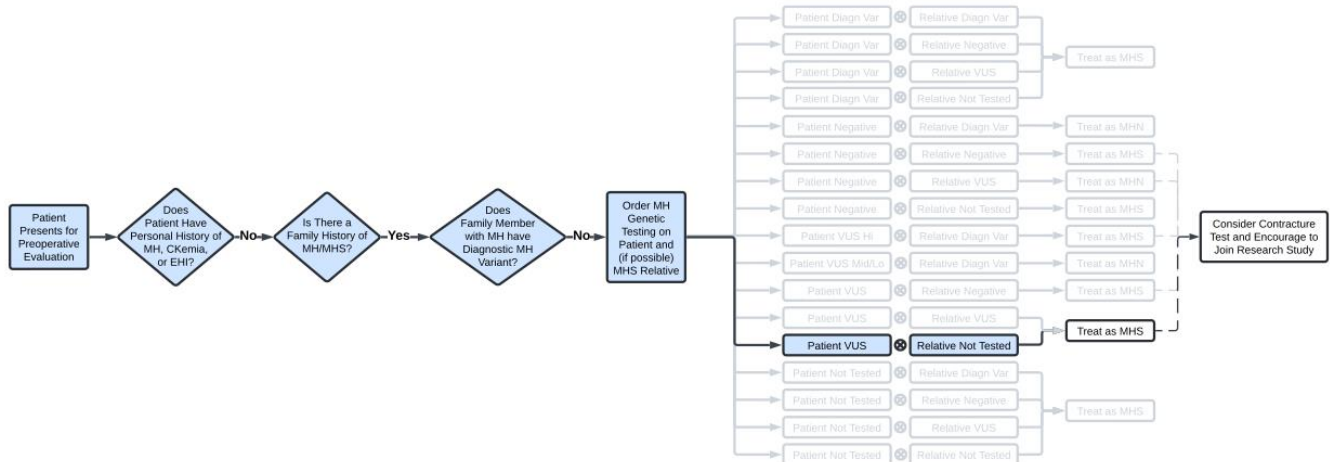


The anesthesiologist orders a three gene (*RYR1*, *CACNA1S*, and *STAC3*) full sequencing MHS gene testing panel on the 8-year-old boy and contacts the family pediatrician to let them know that

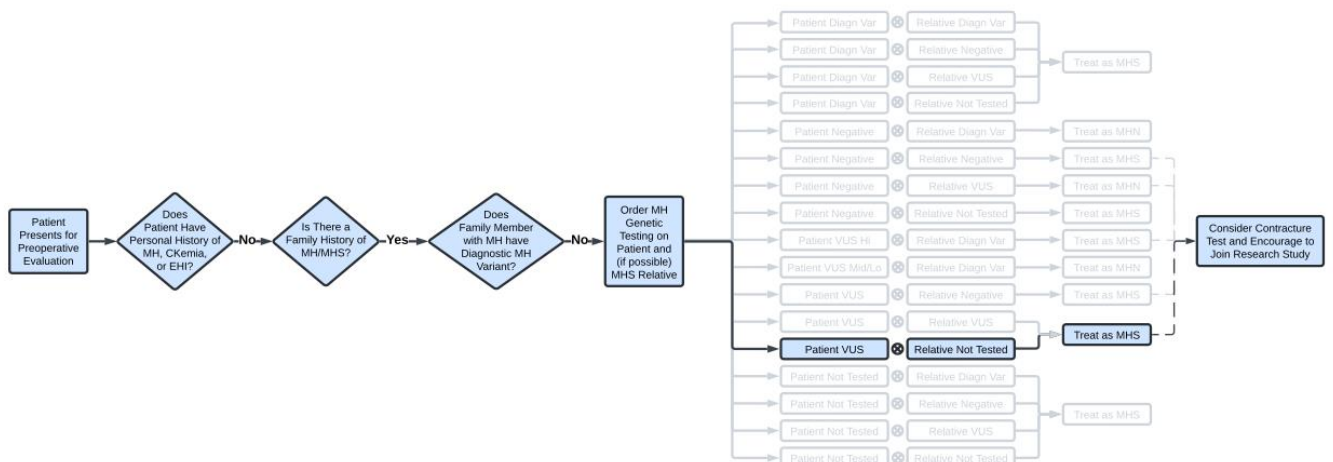
testing on the sister would be highly beneficial not only for her, but additionally helpful in interpreting the results of the boy.



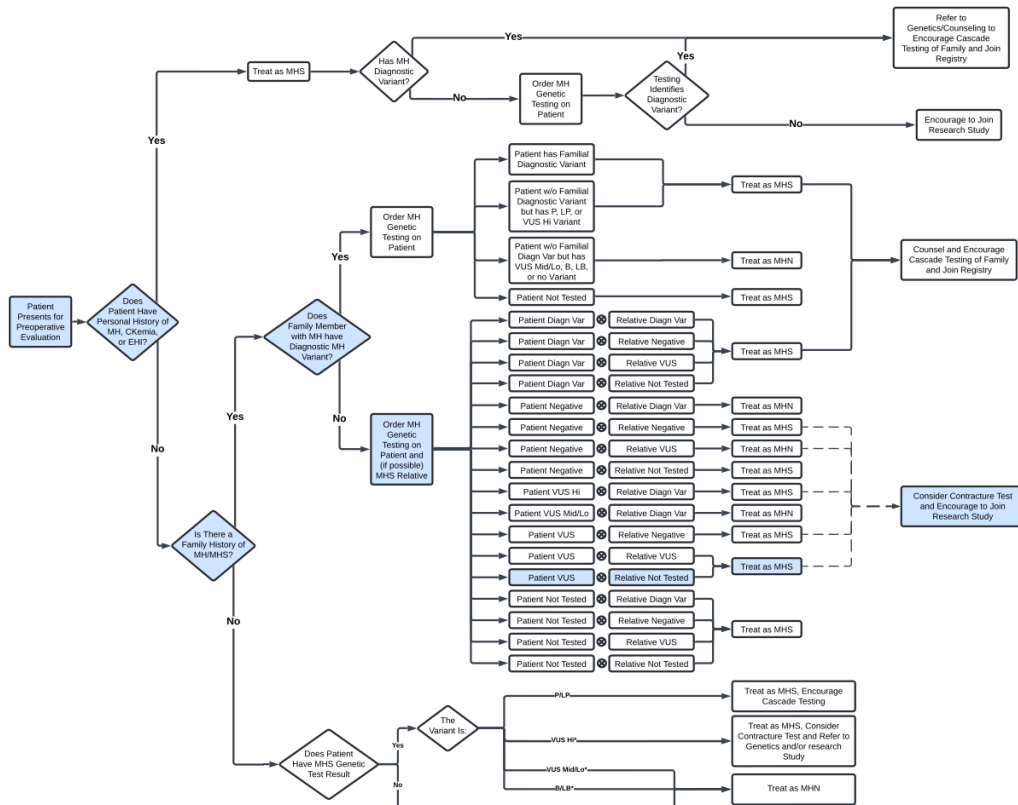
Unfortunately, it was not possible to test the sister in a timely manner. However, the results of the 8 year old boy included the finding of a VUS variant in *RYR1*.



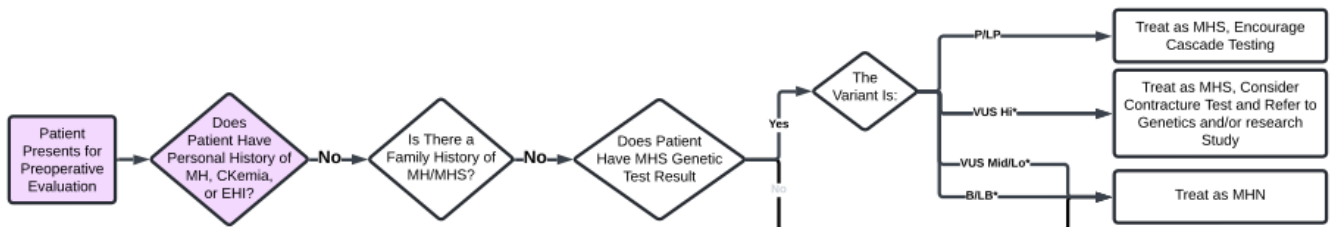
Based on these results, the anesthesiologist elects to perform the case using total intravenous anesthetic, treating the patient as presumptively malignant hyperthermia susceptible and recommends to the family that they enroll him and his sister in a research study and **contracture test** to try to clarify the pathogenicity of the VUS as causative, or to identify an alternative cause of the reaction in his sister.



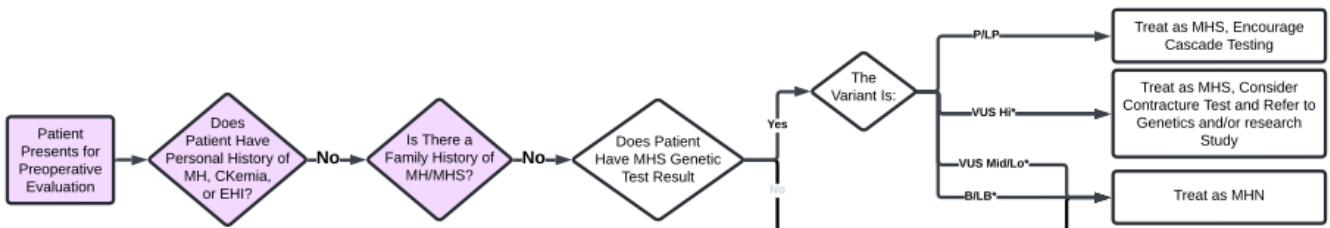
Here is the same logical flow diagram for Scenario 3 in the context of the full flow diagram:



Scenario 4. A 33 year old male presents for preoperative evaluation for elective cholecystectomy. He has no personal history of an MH reaction, CKemia, or exertional heat illness.

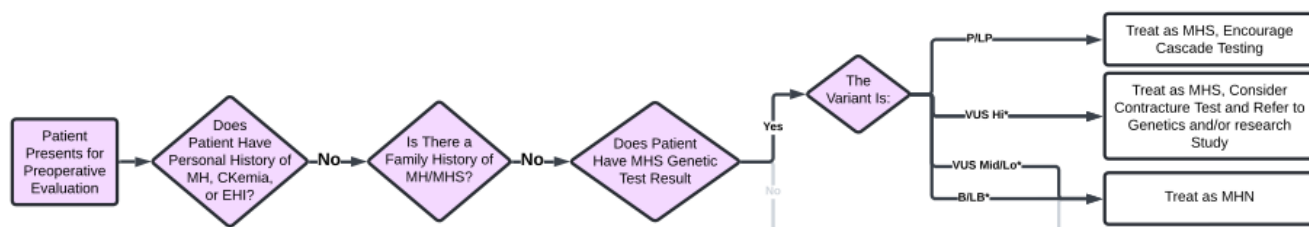


He has no family history of MH or MHS.

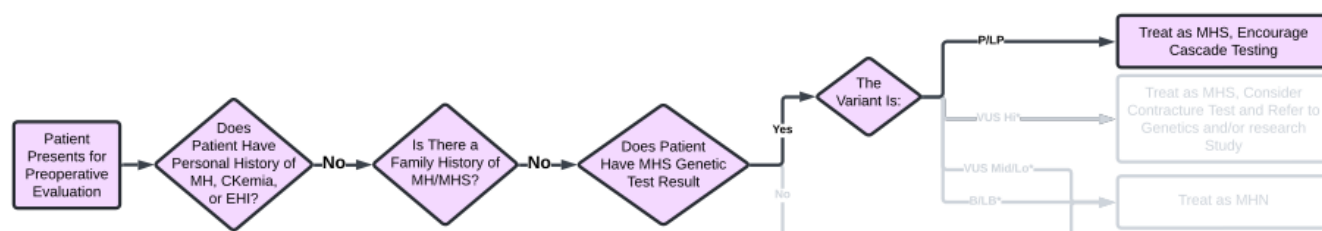


However, he has a 3-year-old child with autism and the family (father, mother, and child) underwent exome sequencing to identify the etiology of the autism, which was not successful. However, per

the standard of care, their exomes were analyzed for secondary findings, and the father was found to have a secondary finding in relevant to MHS.



Because the variant reported as likely pathogenic for MHS, the anesthesiologist elected to do the case using total intravenous anesthetic, recommend cascade testing, and encourage the father to wear a MedicAlert™ identifier.



Here is the same logical flow diagram for Scenario 4 in the context of the full flow diagram:

