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| **About the Measure**  |
| **Domain** | Sickle Cell Disease Curative Therapies |
| **Measure** | Fibrosis Staging of Liver Biopsy |
| **Definition** | Fibrosis staging of a liver biopsy defines the degree of liver scarring and indicates how far disease has progressed. Liver fibrosis is a wound healing response typically resulting from chronic injury, in which the connective tissue matrix is overproduced, inefficiently degraded, or both. Advanced liver fibrosis may lead to the adverse clinical consequences of portal hypertension.There is a high frequency of liver disease in sickle cell disease (SCD) patients who are candidates for curative therapies. Mechanisms of liver injury in SCD include iron overload, vaso-occlusive crises, biliary injury, immune injury, and viral hepatitis (Berry et al., 2007; Feld et al., 2015; Jitraruch et al, 2017; Theocharidou et al., 2019). Advanced liver fibrosis may increase the risk or preclude the use of some curative therapies. |

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| **About the Protocol** |
| **Description of Protocol** | This protocol provides guidance for reporting fibrosis staging of a liver biopsy.  |
| **Protocol** | **Fibrosis Staging**There are several staging systems that are appropriate to measure liver fibrosis. Simple scoring systems, which include three or four categories, are reproducible and are widely used in routine diagnosis and patient management. Complex scoring systems can include seven or more categories. While more complex systems are less reproducible, they provide more information and are useful in studies involving statistical analyses across biopsies. In both simple and complex systems, higher scores imply more severe disease progression. **Recommendations from the Sickle Cell Disease Curative Therapies Working Group (WG)**The WG notes liver staging is comparable regardless of the system used. The WG recommends that the staging system used be reported to enable comparison across studies.  |
| **Participant** | Patients who have had a liver biopsy |
| **Source** | Goodman, Z. D. (2007). Grading and staging systems for inflammation and fibrosis in chronic liver diseases. *Journal of Hepatology, 47*, 598–607.  |
| **Language of Source** | English |
| **Personnel and Training Required** | Fibrosis staging should be performed by an experienced pathologist. |
| **Equipment Needs** | Microscope and liver biopsy sample |
| **Protocol Type** | Physical Measurement  |
| **General References** | Batts, K. P., & Ludwig, J. (1995). Chronic hepatitis: An update on terminology and reporting. *American Journal of Surgical Pathology, 19*, 1409–1417.Bedossa, P., & Poynard, T. (1996). An algorithm for grading activity in chronic hepatitis C. *Hepatology, 24*(2), 289–293.Berry, P. A., Cross, T. J., Thein, S. L., Portmann, B. C., Wendon, J. A., Karani, J. B., Heneghan, M. A., & Bomford, A. (2007). Hepatic dysfunction in sickle cell disease: A new system of classification based on global assessment. *Clinical Gastroenterology and Hepatology, 5*(12), 1469–1476. Desmet, V. J., Gerber, M., Hoofnagle, J. H., Manns, M., & Scheuer, P. J. (1994). Classification of chronic hepatitis: Diagnosis, grading and staging. *Hepatology, 19*, 1513–1520.Feld, J. J., Kato, G. J., Koh, C., Shields, T., Hildesheim, M., Kleiner, D. E., Taylor, J. G., 6th, Sandler, N. G., Douek, D., Haynes-Williams, V., Nichols, J. S., Hoofnagle, J. H., Jake Liang, T., Gladwin, M. T., & Heller, T. (2015). Liver injury is associated with mortality in sickle cell disease. *Alimentary Pharmacology and Therapeutics, 42*(7), 912–921. Jitraruch, S., Fitzpatrick, E., Deheragoda, M., Deganello, A., Mieli-Vergani, G., Height, S., Rees, D., Hadzic, N., & Samyn, M. (2017) Autoimmune liver disease in children with sickle cell disease. *Journal of Pediatrics, 189*, 79–85.Knodell, R. G., Ishak, K. G., Black, W. C., Chen, T. S., Craig, R., Kaplowitz, N., Kiernan, T. W., & Woolman, J. (1981). Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology, 1,* 431–435.Nallagangula, K. S., Nagaraj, S. K., Venkataswamy, L., & Chandrappa, M. (2017). Liver fibrosis: A compilation on the biomarkers status and their significance during disease progression. *Future Science OA, 4*(1), FSO250.Theocharidou, E., & Suddle, A. R. (2019). The liver in sickle cell disease. *Clinical Liver Disease, 23*(2), 177–189.  |