Official Title: Improving Detection and Evidence-based Care of NAFLD in Latinx and Black Patients With Type 2 Diabetes (NAFLD-DM): A Pilot Study

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Background: NAFLD is a critically overlooked T2D complication, and T2D accelerates NAFLD progression to poor outcomes, such as cirrhosis, liver cancer and death.[1, 2] As with other T2D complications**, racial and ethnic disparities exist in detection and care of NAFLD**, although the drivers of these disparities are poorly understood, especially in the context of T2D care.[3] Based on my prior work published in *Hepatology,*[4] there are racial/ethnic disparities in who receives liver biopsy to diagnose NAFLD. For instance, of the 350 patients with T2D who underwent liver biopsy for NAFLD between 2007-2019 in DUHS, only 1.7% and 13% of patients were Latinx and Black, respectively.[4] This is striking when considering that these underrepresented minority groups are disproportionately impacted by T2D complications and poor liver outcomes due to NAFLD.[3] **Because T2D imparts higher risk of poor liver outcomes due to NAFLD,[1, 2] and because underrepresented minority groups are likewise at higher risk of these outcomes, Latinx and Black patients with T2D should be prioritized for proactive detection and intensive management of NAFLD.[5, 6]**

Diabetes care guidelines specifically call for further evaluation of NAFLD in T2D in the presence of abnormal liver enzymes, or when imaging has revealed hepatic steatosis.[6] Detection of high-risk forms of NAFLD is critical in T2D, not only because of the elevated risk of poor NAFLD outcomes in T2D, but also because we can use T2D approaches to effectively treat NAFLD.[5, 7, 8] In a recently published study,[9] we showed that T2D medications that prevent NAFLD progression are vastly underutilized in high-risk patients with T2D. Currently, **disparities in the detection and treatment of NAFLD in patients with T2D are poorly characterized; however, given known racial and ethnic disparities in biopsy rates and NAFLD outcomes, we urgently need to understand disparities in NAFLD detection and care in T2D**. Such data could directly inform the **development of interventions to foster the equitable management of T2D and NAFLD**. To address these critical issues**,** I propose a KL2 program of research that will characterize health disparities in NAFLD detection and care in T2D, and then develop and pilot a culturally-competent intervention that will improve recognition and management of Latinx and Black patients with T2D and NAFLD.

Significance: NAFLD-related liver disease and mortality are high – based on 2015 data, 16.5 million Americans have NASH (i.e., high-risk NAFLD) and mortality in patients with NAFLD is up to 1.27 million annually.[10] These rates are projected to increase by over 130% in the next 10 years.[10] This increased clinical burden will result in direct medical and societal costs of over $300 billion/year.[11, 12] Efforts to prevent this rise in NAFLD complications and costs should focus on populations at highest risk for poor outcomes; thus, this proposal's focus on T2D and high-risk racial/ethnic groups is highly significant. Furthermore, given known health disparities in NAFLD detection, and in T2D care in general, our emphasis on addressing disparities is crucial. This proposal will generate a patient-facing intervention that will improve evidence-based care of NAFLD in T2D, with a focus on reaching Latinx and Black patients who are disproportionately impacted by T2D complications,[13] especially NAFLD.[3] **This work is critically urgent** as the U.S. burden of NAFLD is rising, and several drugs for NAFLD in T2D will come to market soon; this proposal will support equitable use of current and emerging therapies for NAFLD, assuring that those with the greatest need are able to access effective treatment. Because current services are already struggling to reach rising numbers of patients with NAFLD, a major strength of this proposal is its support of **multidisciplinary efforts** to tackle this public health threat.

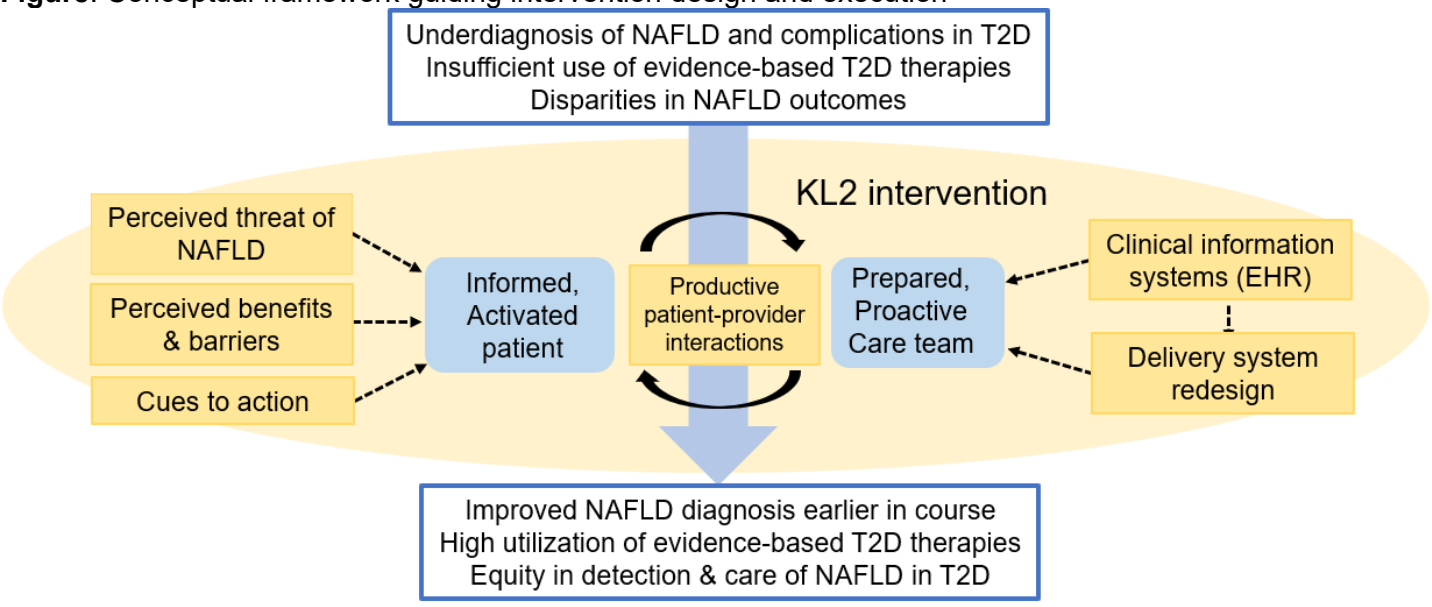
Innovation: This proposal is novel in multiple ways. First, the drivers underlying health disparities in NAFLD detection are poorly understood, and this proposal will address this gap. Second, there are no existing interventions to promote detection and management of NAFLD as part of T2D care, and certainly none to address disparities in these areas. Third, I am proposing an innovative intervention development approach that will leverage community engagement resources at Duke and maximize intervention relevance and feasibility through use of stakeholder input. No studies have queried minority communities to understand how best to design/deliver an intervention to improve outcomes in NAFLD and T2D. Notably, this proposal will proactively improve the care of an exceedingly high-risk, high-cost group through a joint **T2D/NAFLD intervention.** To our knowledge, this will be the first intervention geared towards intensively co-managing these linked conditions.

Research Strategy/Approach

This project will assess the feasibility and acceptability of an intervention for improved detection and evidence-based care of NAFLD in Latinx and Black patients with T2D.

Rationale: Below is a conceptual framework that has guided the design, and will inform the execution, of our intervention. This framework includes features of the Health Belief Model (HBM)[14] to highlight patient-level strategies for disease prevention, and the Chronic Care Model (CCM)[15] to highlight the system-level components aimed at improving the care of NAFLD. As depicted in the Figure below, this intervention represents an innovative approach to ***redesigning care*** and using available ***EHR*** to promote equitable detection of NAFLD (right side of figure). Once detected, we will engage patients with NAFLD and T2D in strategies to promote their overall health and halt, or even reverse their NAFLD. These patient-level approaches will consider how to alter patient perceptions (i.e., ***perceived threat*** of NAFLD, ***perceived benefits & barriers***) and understand patient ***cues to action***, to promote patient engagement with the care plan (left side of Figure). The ultimate objective of this project is to lead to ***productive interactions*** between patients and the care teams (center of Figure) that will ultimately lead to better detection and care of NAFLD in those at highest risk. Prior work has helped us develop this intervention in a culturally-appropriate manner to allow us to reach high-risk racial/ethnic groups with T2D and NAFLD. This will be a feasibility pilot.

Figure: Conceptual framework guiding intervention design and execution



Intervention content and design: The first intervention component will involve proactive detection of NAFLD in Latinx/Black patients with T2D using DEDUCE; this EHR-based approach will allow us to identify eligible study participants in DUHS based on our inclusion/exclusion criteria listed below. The next intervention component will focus on delivery of evidence-based care, which will rely on a proactive care team that is knowledgeable about NAFLD and can intervene, as well as an informed and activated patient who wants to engage with care.

Once identified, patients will receive the following guideline-concordant content as part of the intervention: a) diet/lifestyle support, with counseling on hypocaloric diet and moderate-intensity exercise;[5] b) NAFLD education;[5] c) medication management, with proactive use of T2D medications known to be protective against NAFLD progression (pioglitazone, GLP-1RA, SGLT2i);[5, 7, 16] and d) clinically-indicated liver testing and care based on guidelines.[5] The content of this intervention will be delivered remotely via telehealth approaches. In order to ensure feasibility within the proposed KL2 timeline, we have limited the pilot duration to 3 months. This will allow time to observe change in liver enzymes, as well as HbA1c. Table 1 shows when intervention content will be delivered throughout the

Study population: We will enroll 10-15 Latinx/Hispanic and 10-15 Black patients with T2D and NAFLD, based on elevated ALT and exclusion of other liver diseases (e.g., viral hepatitis, alcohol abuse).

Research activity:

Detection of NAFLD in T2D: The Duke DEDUCE tool will be used to generate a report of potentially eligible Latinx and Black patients with an ICD code for T2D (E11.xx) and at least one ALT >40 IU/mL in males or > 31 IU/mL in females[17] in the preceding 12 months. For this feasibility pilot, we will also restrict eligibility to patients who have a PCP or Endocrinologist in DUHS to facilitate communication regarding T2D medication changes during the study period. We anticipate >2,000 patient will meet our inclusion and exclusion criteria. A report will be exported from DEDUCE and I will review the charts of potentially eligible patients to exclude individuals with liver dysfunction likely due to an etiology other than NAFLD. We will not exclude patients with an ICD-10 code for NASH (K75.81), as long as they are not medically optimized (i.e. on pioglitazone and GLP-1RA), since these individuals serve to benefit from the intervention.

The first 50 patients who meet eligibility will be mailed a letter or sent a MyChart message with opt-out instructions. Patients who do not opt out will be contacted by phone and, if interested, they will sign an e-consent form via REDCap. In parallel to the above recruitment approach, we will also advertise this study in the community with the help of community partners that had assisted us in the design of the intervention, i.e., Latin-19 group and the AME Zion partnership. An IRB-approved flyer (with brief inclusion/exclusion criteria) will be created and placed in community spaces with the help of our community partners. Community members who are interested in the study, and who are also part of DUHS, will be provided with a study contact number to let us know of their interest. We will use the EHR to determine their eligibility, and if eligible, consent will be obtained as above.

Table 1: NAFLD-DM study visits and timing

	Months			
	0	**1**	**2**	**3**
Enrollment, consent review (~20 min, remote visit)	x			
Surveys (~20-30 min, online or on phone)	x			x
NAFLD education (~30 min, remotely)	x			
Diet and lifestyle support (~30 min each, remotely)	x	x	x	
Medication changes (~20 min, remotely) *	o	o	o	o
If indicated, ordering tests and referrals *	o	o	o	o
Interviews (~30 min, remotely)				x

*Timing of med changes and ordering of tests/referrals will vary by participant.
x Visits that will occur for all participants.
o Visits that may or may not occur and are dependent upon individual needs.

Baseline surveys will be conducted by phone or completed online via Duke REDCap. For participants completing surveys by phone, we will ensure that a copy of the survey is mailed or emailed in advance, in case participants prefer to review content in advance. We will survey: self-efficacy,[18] and quality of life surveys[19]). The most recent BMI in the EHR will be used for the purpose of characterizing the participant population – if there is no BMI documented within 1 year of enrollment, we will count BMI data as missing. For HbA1c, if there is no documented HbA1c within 3 months of enrollment to the study, or ALT and ALT within 6 months of enrollment, we will order these tests to be completed at baseline.

Evidence-based care of NAFLD in T2D: Intervention content will include: 1) NAFLD education; 2) diet/lifestyle support; 3) T2D medication management; and 4) clinically-indicated liver testing and care. Dr. Alexopoulos (PI) and the Clinical Research Coordinator (CRC) will deliver NAFLD education and diet/lifestyle support content. Dr. Alexopoulos (PI) will conduct medication management, which will involve review of glycemic trends, assessment of hypoglycemia and adjustment of the T2D regimen to accommodate initiation of pioglitazone, GLP-1RA and/or SGLT2i. The order in which these medications are considered will depend on clinical judgement, patient preference and cost, but GLP-1RA will be prioritized as appropriate, since this class has potent weight loss effects.[16] Also, at baseline (and as indicated throughout the study), Dr. Alexopoulos (PI) will review clinical data and order clinically-indicated liver testing based on guidelines. Surveys and clinical evaluation will be repeated at study conclusion. A treatment acceptability measure (TAP) [20] will be administered at conclusion to gauge intervention acceptability. A detailed summary of data collection and outcome measures can be seen in Table 3.

Table 3: Detailed summary of data collection and outcomes	**Method**	**Timing**
Primary outcomes		
Feasibility		
System-level NAFLD detection	Patients who met criteria for NAFLD after chart review / total number of potentially-eligible patients based on our EHR criteria	3 months
Recruitment rate*	Patients eligible and sent letter or MyChart message / Patients enrolled	3 months
Retention rate	Patients enrolled / Patients completed study	3 months
Visit completion rate	Total study visits completed / total study visits scheduled	3 months
Acceptability		
	TAP measure[20]	3 months
	Qualitative interviews	3 months
Secondary outcomes of interest		
Medication changes made during the study	Study visit notes in EHR	0, 3 months
Proportion of patients in whom clinically-indicated tests were ordered (e.g. labs, referral, imaging).	Study visit notes in HER	0, 3 months
Psychosocial constructs Self-efficacy Autonomy support Quality of life	 6-item SEMCD[21] HCCQ Diabetes[18] SF-12[19]	0,3 months
Descriptive data to characterize population		
Social and demographic Age, sex, race/ethnicity, marital status, education, employment, tobacco use, alcohol use, SDOH screen (food insecurity, housing instability, lack of transportation)	Self-reported surveys	0 months
Health literacy/numeracy	NVS	0 months
Medication adherence	VMNQ[22]	0 months
Clinical Baseline knowledge of NAFLD, years with diabetes, medical history, medication use	Self-reported surveys	0 months

Labs: HbA1c, AST, ALT	Use from EHR if collected within 3 months of baseline visit. Otherwise, research labs collected in DUHS at specified time points.	0 months
Biomedical Height, weight, BMI	From EHR (last recorded values)	0 months

*We will also track the number of participants who expressed interest in the study based on our recruitment flyer, and examine the recruitment rate via this approach (i.e., patients who expressed interest / patients enrolled. **Abbreviations**: TAP=Treatment Acceptability & Preferences; SDOH=social determinates of health; NAFLD=nonalcoholic fatty liver disease; BMI=body mass index; HER=electronic health record; SEMCD=Self-efficacy to Manage Chronic Disease Scale; VMNQ=Voils Medication Non-Adherence Questionnaire; NVS=Newest Vital Sign; HCCQ=Healthcare Climate Questionnaire.

Participant interviews: At study conclusion, individual 30-minute virtual interviews will be conducted with all study participants. The primary purpose will be to assess intervention acceptability and to gain specific feedback about intervention content. Thematic saturation is expected by 12 interviews.[22]

Quantitative analysis: Intervention feasibility will be evaluated by examining recruitment rates, retention rates, and study visit completion rates. For the TAP measure, mean score and standard deviation will be calculated. This feasibility pilot will not be powered to examine changes in clinical measures (e.g., HbA1c, ALT).

Qualitative analysis: All interviews will be digitally recorded and transcribed. Transcripts will be analyzed with direct content analysis.[23]

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