Prioritizing Tuberculosis Genotype Clusters for Further Investigation & Public Health Action

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Purpose

A routine, systematic review of clusters of tuberculosis (TB) cases with matching genotypes can help determine which clusters to prioritize for public health action to interrupt transmission of *Mycobacterium tuberculosis*. This guidance document can assist state, tribal, local, and territorial TB programs in developing policies and procedures for prioritizing TB genotype clusters for further investigation. Prioritization is especially important for jurisdictions where investigating all TB genotype clusters might be too resource intensive.

This guidance document will present background information on TB genotype cluster investigations and why they are important, describe how a program can establish a cluster prioritization process, and suggest considerations for assessing and prioritizing clusters for public health action. To illustrate how a TB program could employ a cluster prioritization system, hypothetical examples and key concepts have been included.

This report was prepared by collaborators of an Outbreak Detection Work Group and CDC's Division of Tuberculosis Elimination.

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For additional information, visit https://www.cdc.gov/tb/ or email tbgenotyping@cdc.gov.

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Overview of TB Genotype Clusters

What is a TB genotype cluster?

A TB genotype cluster can be defined as two or more TB cases[A] with matching genotypes. A cluster definition usually includes place and time components, such as "TB cases with a matching genotype diagnosed in County A during the previous 3 years (for example, in January 2023, cases diagnosed with a matching genotype in County A since January 2020)."

Nationally, a genotype cluster is defined as two or more TB cases[A] diagnosed during a specified 3-year period with *Mycobacterium tuberculosis* (*M. tuberculosis*) isolates that have the same whole-genome multilocus sequence type (wgMLSType). wgMLSTyping is a genotyping scheme that uses whole-genome sequencing (WGS) data. The wgMLSTyping scheme for TB includes 2,690 different genetic loci, each of which is an individual gene in the genome. Isolates that match at ≥99.7% of the loci will form a genotype cluster, designated with a wgMLSType name (formatted as MTBC followed by a 6-digit number). Isolates that are <99.7% identical to any other isolate are designated as MTBCunique. Additional details on whole-genome sequencing and wgMLSType can be found on the Centers for Disease Control and Prevention (CDC) website.[1]

What is a genotype cluster investigation?

A TB genotype cluster investigation is a systematic process to:

- Determine whether a group of TB cases with matching genotypes is related by recent transmission;[B] and
- Identify epidemiological links and potential sites of transmission among patients.

In doing so, it may be possible to identify additional contacts with latent TB infection or TB disease, other opportunities for public health intervention, and false-positive TB cultures.[2]

The relationship between contact investigations, genotype cluster investigations, and outbreak investigations might be unfamiliar to public health practitioners. For additional information on these types of investigations, see Appendix B.

A. Tuberculosis case definition available online at https://ndc.services.cdc.gov/case-definitions/tuberculosis-2009/

B. Recent transmission of *Mycobacterium tuberculosis* is typically defined as transmission occurring in the 2-3 years prior to diagnosis of the given case.

Why prioritize genotype clusters?

A key goal of the prioritization process is to identify clusters of concern due to the

- Likelihood that patients in a genotype cluster are related by recent transmission; **and/or**
- Likelihood of ongoing or future transmission.

Cluster prioritization can help a health department focus resources on where interventions can have the greatest impact, benefiting individual patients and the larger community. Considerations for prioritizing cluster investigations will vary but should always be consistent with local public health priorities and available resources. TB cluster investigations should not take precedence over treating TB disease and conducting contact investigations, although cluster investigation results can inform these and other core TB control activities.

Additionally, not all TB clusters require further investigation; a quick review of available data might determine that a cluster is a low priority for further investigation or public health action. However, cluster prioritization is a dynamic and ongoing process. Assessments of a cluster can change with new information or if additional genotype-matched cases are identified.

Establishing a Cluster Prioritization Process

Health departments can improve their ability to respond to genotype clusters by establishing a cluster prioritization process and planning how the program will respond to each priority level.

This process should also involve outlining in advance who will be involved in the prioritization process and how they will respond. The cluster review process will vary across programs and depend on multiple factors, including the jurisdiction's TB incidence and epidemiology, staff resources, and program organization. However, collaboration and communication between state and local TB programs and other stakeholders are a crucial component to successfully assessing TB clusters. The following is an outline of considerations for establishing a process to review and prioritize cluster investigations.

Identify key staff and establish roles

- Identify person(s) responsible for routine review of genotyping data and clustered cases.
- Identify key personnel and communication processes for cluster assessment and prioritization, additional decision-making, and related resource allocation and communication.

In some jurisdictions, the state TB genotyping coordinator will routinely review all new or growing genotype clusters. A larger team may be convened on a recurring basis or as needed to discuss clusters of concern, coordinate additional information gathering, and establish related action items.

Determine how to identify clusters

- Genotype clusters may be identified in several ways, including:
  - Discussions with local health department staff and other partners who suspect new clusters before genotyping results are available.
  - Use of TB Genotyping Information Management System (TB GIMS) to
    - Routinely identify and review all clusters in a jurisdiction;
    - Selectively review those county-based clusters that have generated TB GIMS alerts; and
    - Create personalized notifications through a TB GIMS watch list.
  - Monitoring of genotypes associated with prior or current outbreaks to detect growing clusters that might represent a new outbreak or other recent transmission.
  - Creation of local or state algorithms to detect clustering of TB cases geographically and in a given time frame.
  - Discussions with CDC about clusters of concern identified through other means, such as SaTScan, a software that analyzes spatial concentrations of cases without regard for territorial boundaries.

Establish key criteria for cluster review, review frequency, and prioritize for public health action

- Determine which clusters will be reviewed.
  - Some jurisdictions may review all genotype clusters; others might choose to focus on new or growing clusters or on TB GIMS-alerted clusters.
  - All jurisdictions should consider reviewing previously identified clusters when new cases are added.

- Determine how often clusters will be reviewed. Clusters may be reviewed:
  - At regular intervals (for example, weekly or monthly),
  - Whenever a new cluster generates an alert,
  - Whenever new genotyping results are available, or
  - Upon request from federal, state, or local programs.
- Develop a tiered system that clearly defines cluster priority levels and corresponding action steps.
  - One example is a 3-tiered priority system, as described in Table 1.
  - Alternatively, some programs might prefer a simpler 2-tiered approach (investigation warranted, investigation not warranted at this time).

TABLE 1: Example Cluster Prioritization System

Priority Level	Description	Potential Actions
Priority 1	▸ Clusters with *multiple* characteristics indicating possible recent transmission,[C] ▸ *Multiple* characteristics associated with poor patient outcomes, and ▸ Cases are recent enough that public health intervention is possible.	Review available data with stakeholders and *actively* seek additional information.
Priority 2	▸ Clusters with *some* characteristics indicating possible recent transmission, ▸ *Some* characteristics associated with poor patient outcomes, and ▸ Cases are recent enough that public health intervention is possible.	Monitor for additional cases with a matching genotype, or clinical cases that may share characteristics with other cases in the cluster.[D]
Priority 3	▸ Clusters with *minimal or no* characteristics indicating possible recent transmission, ▸ *Minimal or no* characteristics associated with poor patient outcomes, and ▸ Cases are *not* recent enough that public health intervention is possible.	No additional public health action indicated at this time.

C. See the section titled "Considerations for Prioritizing Cluster Investigations" for additional information on characteristics indicative of recent transmission.

D. Consider monitoring for additional cases matching the genotype of interest by using a "watch list" feature and periodically reviewing the TB GIMS National Distribution Report.

Considerations for Prioritizing Cluster Investigations

The decision to prioritize a genotype cluster for investigation is multifactorial. The following sets of questions can help frame key considerations for prioritizing cluster investigations.

Determine if the cluster likely represents recent transmission

- Are the WGS data consistent with recent transmission? (Refer to the call-out box below for additional considerations)
- Are there known or suspected epidemiologic links among cases in the cluster?
- Is the cluster comprised of cases with a new genotype in the county or state?
- Is it the same genotype as a known outbreak?
- Has the cluster grown rapidly in the past 2–3 years?
- Does the cluster include cases occurring in children under 5 years of age?
- Do patients in the cluster have evidence of recent infection (for example, tuberculin skin test conversions or interferon-gamma release assays)[E] or clinical factors suggestive of recent infection (for example, HIV infection or other immunocompromising condition)?
- Is the genotype rare nationally?

E. For more information, consult the following references: Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis and Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection.[3,4]

Use of whole-genome single nucleotide polymorphism (wgSNP) comparison for investigation of recent transmission

Although genotyping helps identify clusters that may represent recent TB transmission, these methods have limitations. Genotype clustering can occur among cases that are not related by recent transmission, especially for genotypes that are longstanding or common in a particular geographic area. Whole-genome single nucleotide polymorphism (wgSNP) comparison of WGS data investigates a larger (~90%) portion of the *M. tuberculosis* genome, increasing the molecular resolution for determining relatedness of cases. wgSNP comparison uses WGS data to identify single nucleotide polymorphisms (SNPs) that distinguish isolates in a genotype-matched cluster. SNPs result from mutations at a single position in the DNA sequence. The SNPs identified in a wgSNP comparison can be mapped onto a phylogenetic tree to diagram the genetic relationship among isolates. The number of SNPs that differ between isolates can be used in combination with available epidemiologic and clinical data to help assess whether TB cases are related by recent transmission. Based on DTBE's experience, isolates within ≤5 SNPs are considered genetically close and are more likely to be involved in the same chain of recent transmission. A guide to interpreting a phylogenetic tree is available in Appendix C.

wgSNP comparison may provide additional information that can inform public health action by:

- Providing increased molecular resolution for a cluster of cases with a wgMLSType that is common in the population or area;
- Identifying a subset of cases for which recent transmission is more likely to be occurring to inform cluster or outbreak investigation;
- Providing additional information that can distinguish cases attributable to recent transmission from cases that are due to reactivation of latent TB infection; and
- Helping avoid misdirecting public health resources to investigate genotype clusters of cases that might not be linked by recent transmission.

Identify characteristics concerning for cluster growth or poor patient outcomes

- Is there evidence to suggest that transmission is ongoing? For example, are there multiple cases in the previous 12 months?
- Do recent patients in the cluster have positive sputum smears or cavitary lung lesions (suggesting a higher degree of infectiousness compared to sputum smear-negative and non-cavitary patients)?
- Did any recent patients have long infectious periods before diagnosis?
- Is a homeless shelter, correctional institution, or other congregate setting involved?
- Do patients have risk factors, such as substance use, that can be associated with difficult or incomplete contact investigations?
- Do patients and their contacts have similar risk factors that suggest an increased risk for disease progression, such as human immunodeficiency virus (HIV) or renal failure?
- Do any patients have drug-resistant TB?
- Were any cases found among contacts missed by previous contact investigations? Could other contacts have also been missed?
- Have patients in the cluster died with TB as the cause or contributing factor of death?
- Were any cases among persons previously identified as contacts but not fully evaluated or treated? Could other contacts be at risk?
- Are epidemiologic links among patients unclear or not identified, or is there reason to suspect that contact investigations have not been adequately thorough?

Example of how to assess a genotype cluster for recent transmission and characteristics concerning for cluster growth

The following is an example of how a TB program might assess a genotype cluster for recent transmission and characteristics concerning for cluster growth or poor patient outcomes. The County A TB program noticed a recent increase in cases with MTBC123456, a genotype nationally unique to their jurisdiction, and decided to review characteristics of the associated cases to determine if recent transmission or cluster growth was likely.

FIGURE 1A: Line list of select patient characteristics and TB risk factors useful for assessing the likelihood of recent transmission, MTBC123456, County A, 2018–2023

Case	Count Date	Sex	Age	Race/Ethnicity	Origin of Birth	HIV	Known Epi Links
Case 5	**11/10/2023**	F	**1**	**Black**	U.S.-born	Negative	**Family member to Case 4**
Case 4	**10/16/2023**	M	29	**Black**	U.S.-born	**Positive**	**Family member to Case 5**
Case 3	**05/15/2023**	F	32	Asian	Non-U.S.-born	Negative	None
Case 2	01/20/2020	M	41	Asian	Non-U.S.-born	Negative	None
Case 1	04/08/2018	M	28	Asian	Non-U.S.-born	Negative	None

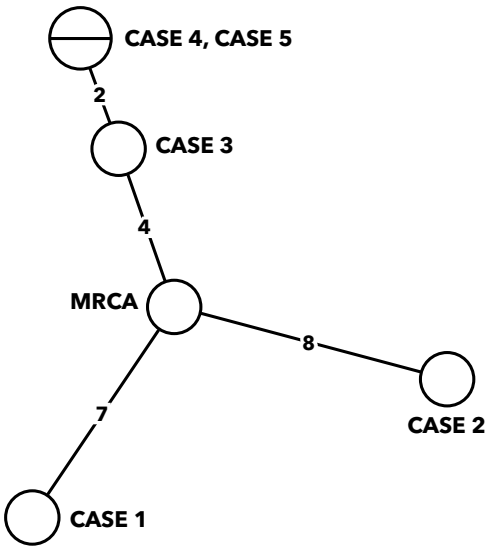
In reviewing the line list of cases in Figure 1A, there is evidence of recent transmission among the recent cases. Note the diagnosis of TB in an infant and a patient with HIV infection. These cases are family members and are known to be epidemiologically linked to each other. Additionally, the recent increase in the number of cases with this genotype and a shift in demographics increases suspicion of recent transmission.

In continuing to review, the program also noticed patient characteristics concerning for cluster growth. Cases 3 and 4 both had clinical markers of highly infectious TB (positive sputum smears and cavitary lesions) and TB risk factors concerning for cluster growth (HIV, substance use, and homelessness). See the line list of select patient characteristics and TB risk factors in Figure 1B.[5]

FIGURE 1B: Line list of patient characteristics and TB risk factors useful for assessing characteristics concerning for cluster growth or poor patient outcomes, MTBC123456, County A, 2018–2023

Case	Sex	Age	Count Date	Pulmonary Disease	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless	Known Epi Links
Case 5	F	1	11/10/2023	No	Not Done	No	None	Negative	No	No	No	Family member to Case 4
Case 4	M	29	10/16/2023	**Yes**	**Positive**	**Yes**	None	**Positive**	**Yes**	No	**Yes**	Family member to Case 5
Case 3	F	32	05/15/2023	**Yes**	**Positive**	**Yes**	None	Negative	**Yes**	No	No	**None**
Case 2	M	41	01/20/2020	Yes	Negative	No	None	Negative	Yes	No	No	None
Case 1	M	28	04/08/2018	Yes	Positive	Yes	None	Negative	No	No	No	None

FIGURE 1C: Phylogenetic tree depicting genetic relatedness among isolates with MTBC123456



While an epidemiologic link was identified between the pediatric case (Case 5) and an adult TB case (Case 4), there is no known connection to the other recently diagnosed case with this genotype (Case 3). Given the increased likelihood of recent transmission and concerning characteristics of this cluster, the jurisdiction requested a wgSNP comparison of all isolates to help determine which cases may be involved in recent transmission (Figure 1B). Refer to the call-out box below for how to request wgSNP comparison.

Despite no known epidemiologic links, isolates from Cases 3 and 4 were found to be 2 SNPs apart, which suggests recent transmission between these cases. The wgSNP comparison results for Case 4 and 5 were 0 SNPs apart, which is consistent with the known epidemiologic link (between adult

and infant). The genetic similarity among isolates from Cases 3, 4, and 5 and the rarity of the genotype indicate there is likely a connection between the three recently diagnosed cases. Based on their review, TB program staff at County A opened a cluster investigation for these three cases.

Requesting a wgSNP comparison

All TB GIMS cluster alerts are analyzed using wgSNP comparison. In addition, a wgSNP comparison for any clustered isolates in your jurisdiction can be requested. If a cluster investigation would benefit from wgSNP comparison, consult with appropriate TB program officials in your jurisdiction. Importantly, data collected during epidemiological investigations are always needed to accurately interpret WGS results and identify likely transmission among patients. Older isolates that were genotyped prior to the start of prospective whole-genome sequencing in 2018 can sometimes be included in a wgSNP comparison upon request. Requests for wgSNP comparison can be made through TB GIMS. To consult about a genotype cluster alert, or if you need assistance requesting a wgSNP comparison, you can email: tbgenotyping@cdc.gov.

Additional considerations

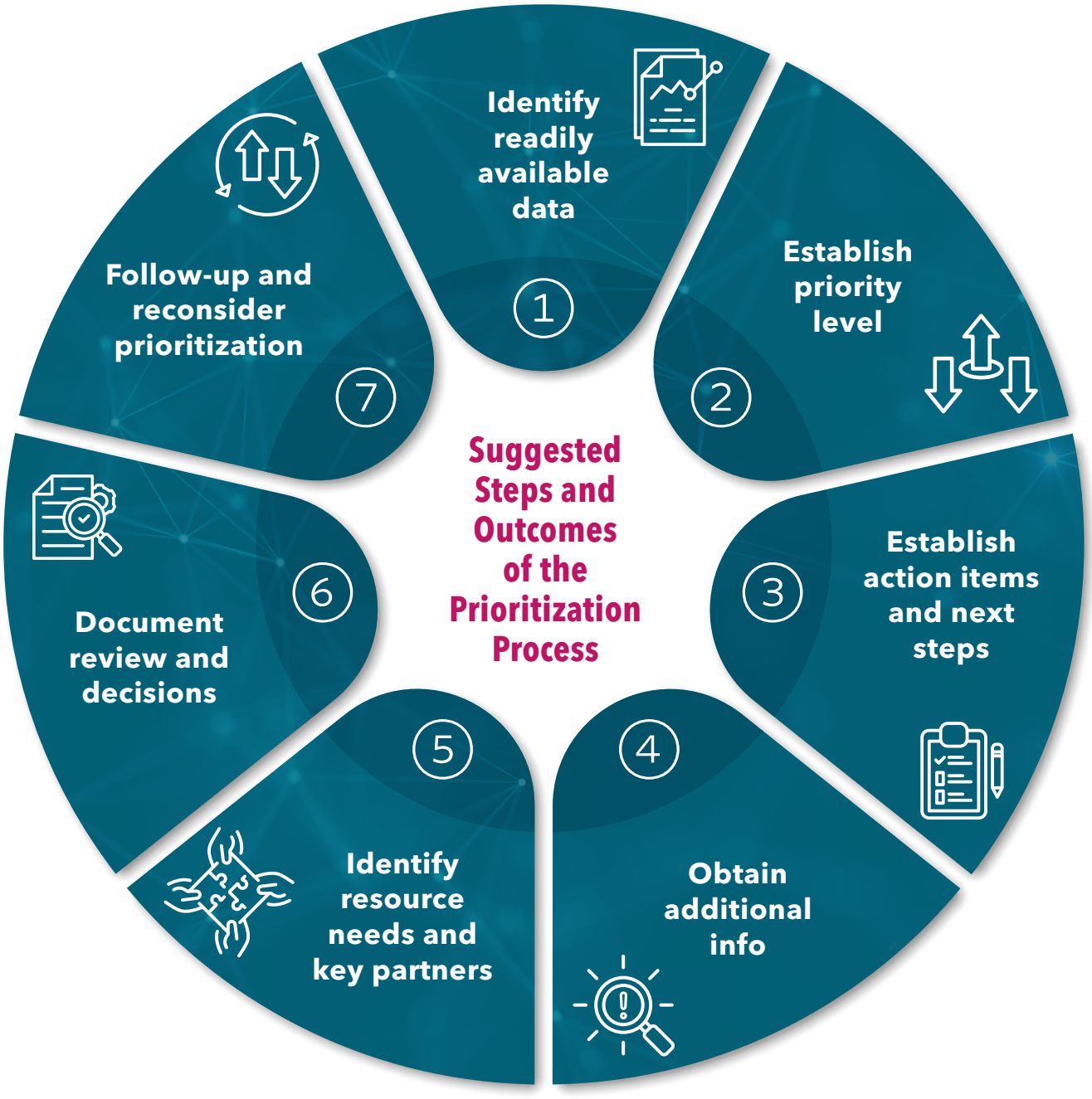
- The cluster review process should also consider non-genotyped or clinical TB cases that may be related to the cluster. Consult TB GIMS or other local surveillance databases for non-genotyped cases in the same time frame and geographic area that have similar demographic and clinical characteristics as cases in the cluster of interest.
- Consider consulting the National Distribution Report in TB GIMS if there is concern that additional related cases with the genotype of interest have occurred in other jurisdictions. Discuss the possibility of epidemiologic linkages with the state TB program or CDC as appropriate, especially if the genotype is rare (meaning it is not commonly seen nationally).
- The National Surveillance Summary is an additional report summarizing the demographic and clinical characteristics of patients with the genotype of interest. This information can be a useful reference when considering the epidemiologic characteristics of cases in your jurisdiction.

- About two-thirds (65%) of all wgMLSType county-based clusters are made up of only two cases. State and local TB programs may choose to prioritize two-case clusters under specific circumstances such as:
  - At least one of the patients has multidrug-resistant TB;
  - At least one of the patients is less than 5 years old;
  - The wgMLSType is rare and both patients reside in the same local areas;
  - One or more patients have locally identified characteristics of concern such as a shared setting where transmission is suspected; or
  - False-positive culture results are suspected for one of the cases.

False-positive culture results can occur due to cross-contamination or mislabeling during specimen collection or during processing in the laboratory. Laboratory cross-contamination has been reported to occur in up to 3% of *M. tuberculosis* isolates.[6] To detect false-positive TB culture results, some jurisdictions will routinely review specimen collection and laboratory processing dates for all patients in new genotype clusters. Cross-contamination should be considered when *M. tuberculosis* is cultured from a patient specimen that is collected on the same date or processed in the same batch as another specimen (especially when a patient does not have symptoms consistent with TB). If there is a suspicion that laboratory results may be the result of an error, discuss with laboratory partners and other appropriate stakeholders. Detecting and identifying false-positive culture results can avoid unnecessary TB treatment and unwarranted cluster investigations. Additional information on investigating false-positive culture results has been described elsewhere.[7,8]

Suggested Steps and Outcomes of the Prioritization Process

The following steps are intended as a guide for identifying, reviewing, and prioritizing TB genotype clusters. The sequence of steps and extent to which the steps are conducted may differ depending on each genotype cluster and should be based on available resources and prioritization of clusters.



Step 1: Identify readily available data sources for genotype cluster review

TB GIMS provides patient-level information (for example, demographic, clinical, and social characteristics) from the National TB Surveillance System, as well as the local, state, and national distribution of the cluster's genotype.

Additional data sources that may be readily available include:

- A new or updated wgSNP comparison;
- State and local surveillance data and/or case management databases;
- Existing interview notes and contact investigation records for cases;
- Case managers, directly observed therapy workers, clinicians, laboratorians, or other health department staff who interact most closely with the patients; and
- Any other relevant records, such as past investigations of the cluster.

Step 2: Establish the current priority level of the cluster

After review and discussion with stakeholders, assign a priority level for the cluster (example prioritizations are described in Section III C above). This determination should be based on the likelihood for recent transmission in the jurisdiction and the level of concern for future growth.

Step 3: Establish action items and next steps

Decide whether public health intervention is indicated (actively seeking additional information that is not readily available). If intervention is not indicated, it may be possible to progress to Step 6 below (skip Steps 4 and 5).

If intervention is indicated, consider the following potential next steps:

- Identify the most likely source case(s).
- Review and potentially expand the contact investigation around known source cases.
- Ensure contacts have been fully evaluated and treated.
- Conduct patient reinterviews and record searches to identify additional contacts and exposure sites that warrant further follow-up.

- Utilize incentives and enablers and field-based services to help ensure contact follow-up and treatment.
- Assign responsibilities for next steps based on the locally established cluster prioritization system, including roles, expectations, and timeline for reconvening to discuss further.
- Consider if additional communication with stakeholders would be helpful, such as frontline staff who may be aware of potential epidemiological links between seemingly unrelated patients. If warranted, identify who should lead the communication efforts.

Step 4: Obtain additional information that is not readily available

To actively seek additional information, consider the following approaches:

- Discussions with frontline TB staff;
- Conduct patient re-interviews;
- Re-review medical records; and
- Conduct other record searches as appropriate (social media,[F] fee-based online record searches,[G] and other social service databases).[H]

In some jurisdictions, the state TB genotyping coordinator might examine all the genotyping, surveillance, and contact investigation data available at the state level, and then determine whether additional investigation is warranted.

Example outcomes from the cluster prioritization process

Due to the concerning factors identified in the MTBC123456 cluster, County A TB program staff convened a case review meeting with frontline staff, clinic staff, epidemiologists, and the program manager. During the case review, staff were able to identify a previously unrecognized epidemiologic link between Cases 3 and 4. Based on this information, the County A TB program initiated a review of the contact investigations for Cases 3 and 4 and possible sites of transmission. Case 3 was determined to have a previously unrecognized history of homelessness in a local homeless shelter where Case 4 resides. The County A TB program should initiate a contact investigation in the local homeless shelter where transmission has been linked between Case 3 and Case 4, prioritizing contacts most at risk for progression to TB disease. They should further

F. Social media searches to consider include: Facebook, Twitter/X, Instagram, dating websites, and other person-search databases (for example, Google). Use of brand names is for illustrative purposes and does not imply endorsement.

G. Fee-based online record search services are available that can provide additional information that may be useful in identifying epidemiological links among patients.

H. Social service databases to consider include: jail/prison databases, homeless shelter databases such as the Homeless Management Information System (HMIS), and healthcare facility databases.

investigate any potential contacts of Case 3 and Case 4 and consider initiating a source case investigation for Case 5. These efforts can help identify additional persons who would benefit from TB evaluation and treatment.

Although TB programs define an epidemiologic link between two patients differently, the process of identifying epidemiologic links may help TB program staff better understand how, where, and when transmission may have occurred. By understanding how patients are epidemiologically linked, transmission patterns can be identified, and public health interventions can be implemented. Additional information on epidemiologic links, transmission links, and how they relate to TB outbreak investigations can be found in CDC's Self-Study Module 9: Tuberculosis Outbreak Detection and Response.[9]

Step 5: Identify resource needs and key partners

- What level and types of resources will the health department need to investigate the cluster? To intervene?
- If the cluster involves a challenging or difficult-to-access population (such as people who use substances, inmates in correctional facilities, and persons experiencing homelessness), consider identifying key stakeholders and community resources that could be of assistance. These could include homeless shelters, community representatives, and advocacy organizations.

Step 6: Document review and decisions

Develop a systematic method for documenting cluster assessments and actions taken. This could be accomplished by maintaining a simple cluster tracking tool in a spreadsheet or text document. Consider capturing the following information:

- wgMLSType,
- Results of wgSNP comparison (if applicable, including if the results are consistent with recent transmission),
- Jurisdiction(s),
- Identification method (for example, notification from local health jurisdiction, TB GIMS LLR alert, TB GIMS watch list notification for previously identified cluster),

- Date of first identification,
- TB GIMS alert level (if applicable),
- Most recent date of team assessment,
- Most recent team assessment of the cluster (the priority level), and
- Public health action taken, if warranted.

A sample tool for tracking TB cluster assessments is shown in Figure 2. TB program staff developed a spreadsheet to track known clusters in their jurisdiction. In the spreadsheet, staff document when and how the cluster was identified, the team's assessment, and any associated action steps based on the cluster prioritization.

FIGURE 2: Example of a Cluster Tracking Tool, County A

wgMLSType	Jurisdiction	Identification Method	Date of Detection	Alert Level	Most Recent Date of Team Assessment	Findings	Team Priority Assessment	Notes
MTBC123456	County A	TB GIMS LLR alert	11/13/2023	TB GIMS Medium Alert	11/15/2023	Consistent with recent transmission	Priority 1	Cluster investigation initiated
MTBC987654	County A	Contact Investigation of Case	2/1/2023	Not Applicable	2/3/2023	Consistent with recent transmission	Priority 2	Monitoring cluster with watch list
MTBC654123	County A	Routine Review of New Genotype Results	1/20/2023	Not Applicable	1/25/2023	Not consistent with recent transmission	Priority 3	Cases in common genotype, wgSNP rules out transmission

Step 7: Follow up and reconsider cluster prioritization as applicable

Follow up on action items and review new cases or additional information as it becomes available. For example, reconsider the cluster priority when:

- Additional wgMLSType-matched cases are diagnosed, especially when there are more recent cases than expected,
- Updated wgSNP comparison results are consistent with recent transmission,
- Common demographic characteristics or shared settings are identified or demographic characteristics of cases in the cluster change (for example, shift from non-U.S.–born persons to U.S.-born persons), or
- Cases with resistance to additional TB medications are detected.

Based on the availability of resources, determine which cluster priority levels warrant re-review.

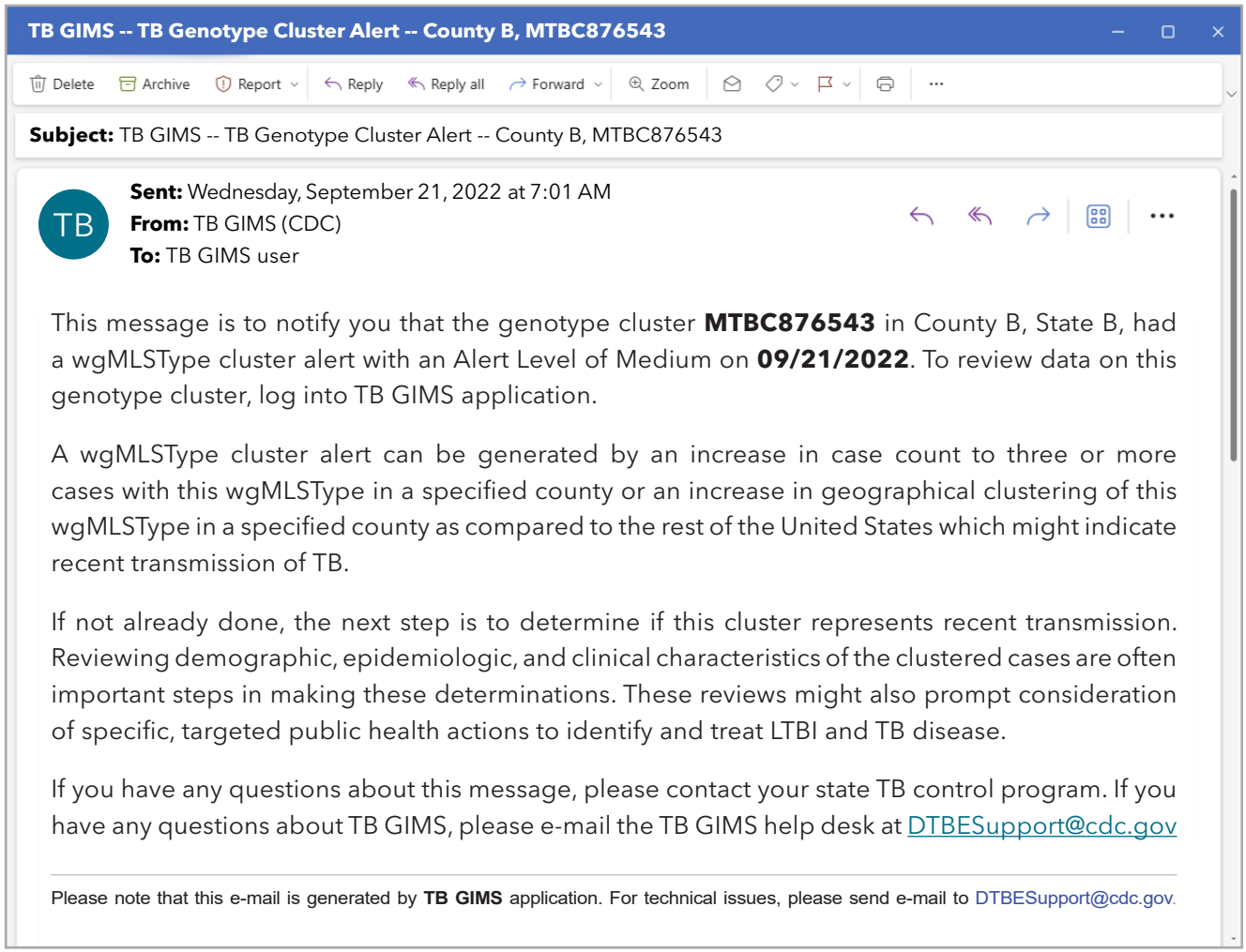
Examples of Prioritizing Genotype Clusters

Example 1: Assessment of a Priority 3 cluster in County B, a jurisdiction with TB incidence higher than the national average

County B has a population of approximately 600,000 people primarily living in one city in the county, and typically reports about 40 TB cases per year. In 2021, the county reported 43 TB cases, corresponding to 6.1 cases per 100,000 persons, which was higher than the national average (3.0 cases per 100,000 persons).

On September 21, 2022, County B received a TB GIMS alert for MTBC876543 with a medium alert level (Figure 3).

FIGURE 3: Sample email for a TB GIMS cluster alert for wgMLSType MTBC876543 in County B



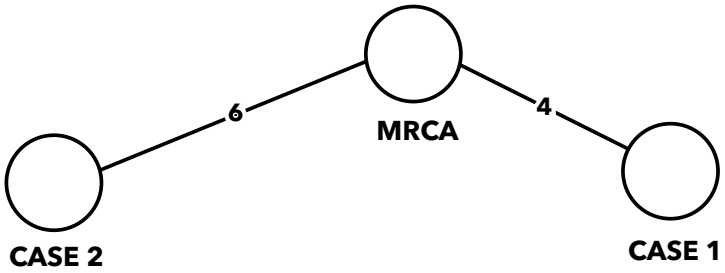
During the regularly scheduled cluster review meeting, TB staff in County B determined this alert was generated based on two cases—one in 2021 and one in 2022. Both were non-U.S.–born patients living in the same neighborhood, indicating a possible epidemiologic link. To assist in the review of genotype clusters, staff routinely develop line lists of known clinical and epidemiological information (Figure 4A).

FIGURE 4A: Line list of patient characteristics and TB risk factors, wgMLSType MTBC876543, County B

Case	Count Date	Sex	Age	Race/ Ethnicity	Origin of Birth	Pulmonary Disease	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless	Known Epi Link
Case 2	9/13/2022	M	52	Asian	**Non-U.S.-born**	**No**	**Negative**	**No**	None	Negative	No	No	No	**Same neighborhood as Case 1**
Case 1	12/23/2021	M	34	Asian	**Non-U.S.- born**	**No**	**Negative**	**No**	None	Negative	No	No	No	**Same neighborhood as Case 2**

Despite the potential for contact due to living in the same neighborhood, wgSNP comparison (Figure 4B) found these isolates to be 10 SNPs apart, making recent transmission unlikely. Since there was a lack of clinical characteristics consistent with highly infectious TB (such as positive sputum smears or cavitary lesions) or other TB risk factors for cluster growth, TB program staff utilized the pre-defined prioritization system to designate this cluster as a Priority 3, indicating that no further cluster investigation is necessary at this time.

FIGURE 4B: Phylogenetic tree depicting genetic relatedness among isolates with MTBC876543



Key concepts from Example 1

- Assess a TB GIMS alert during recurring cluster meetings,
- Utilize wgSNP comparison results to assess the likelihood of recent transmission,
- Utilize a pre-defined cluster prioritization system during the review process (for example, Priority 1, Priority 2, and Priority 3), and
- Identify as a Priority 3 cluster and close public health follow-up at this time based on low suspicion for ongoing transmission.

Example 2: Assessment of a Priority 2 cluster in County B

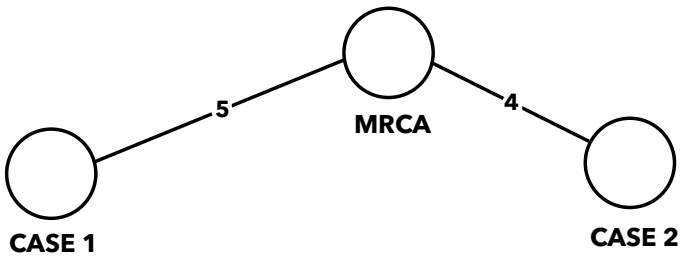
On July 20, 2022, County B received a TB GIMS alert for wgMLSType MTBC456789 with a medium alert level. During the regularly scheduled cluster review meeting, TB staff determined the alert was generated based on 2 cases: one in 2021 and one in 2022. Upon review of their developed line list, staff identified that both cases were U.S.-born Hispanic males who had no reported social risk factors (Figure 5A). However, both cases had isoniazid-resistant TB, and the most recent case had pulmonary, sputum-smear positive disease.

FIGURE 5A: Line list of patient characteristics and TB risk factors, wgMLSType MTBC456789, County B

Case	Count Date	Sex	Age	Race/ Ethnicity	Origin of Birth	Pulmonary Disease	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless	Known Epi Link
Case 2	7/18/2022	M	42	Hispanic	U.S.-born	**Yes**	**Positive**	No	**Isoniazid**	Negative	No	No	No	None
Case 1	2/8/2021	M	68	Hispanic	U.S.-born	No	Negative	No	**Isoniazid**	Negative	No	No	No	None

Based on the national distribution report in TB GIMS, staff recognized MTBC456789 to be unique to County B. Review of the wgSNP comparison results (Figure 5B) showed that the isolates from the two patients were 9 SNPs apart. While the SNP distance between the isolates lowers the likelihood that the cases are related by recent transmission, one of the patients has infectious, drug-resistant TB. Therefore, the review team determined this cluster should be assigned a Priority 2, indicating no additional cluster investigation is warranted at this time but that they should review the contact investigation for Case 2 for completeness and additional opportunities for contact evaluation and treatment. In addition, the team decided to monitor for additional cases in the future given the drug resistance.

FIGURE 5B: Phylogenetic tree depicting genetic relatedness among isolates with MTBC456789



To assist with monitoring this cluster, a staff member was assigned the task of creating a TB GIMS watch list for MTBC456789 in County B (Appendix Figure 3). In the future, the TB GIMS user who created the watch list item will receive a notification (through TB GIMS or via email) if a new case has a matching wgMLSType in County B. This notification will help prompt the TB program staff to reassess the prioritization of this cluster.

TB program staff also wanted to monitor for clinical or non-genotyped cases with similar characteristics that may be related to this cluster. To review these cases, staff can view clinical or non-genotyped cases using local databases or through TB GIMS (Appendix Figure 4).

To assist in monitoring for cases with a matching wgMLSType outside of their jurisdiction, TB program staff could create a national-level watch list. Given this is a unique wgMLSType in their jurisdiction, this national-level watch list would alert staff to cases that may be diagnosed outside of their jurisdiction, but that may be related to their cluster.

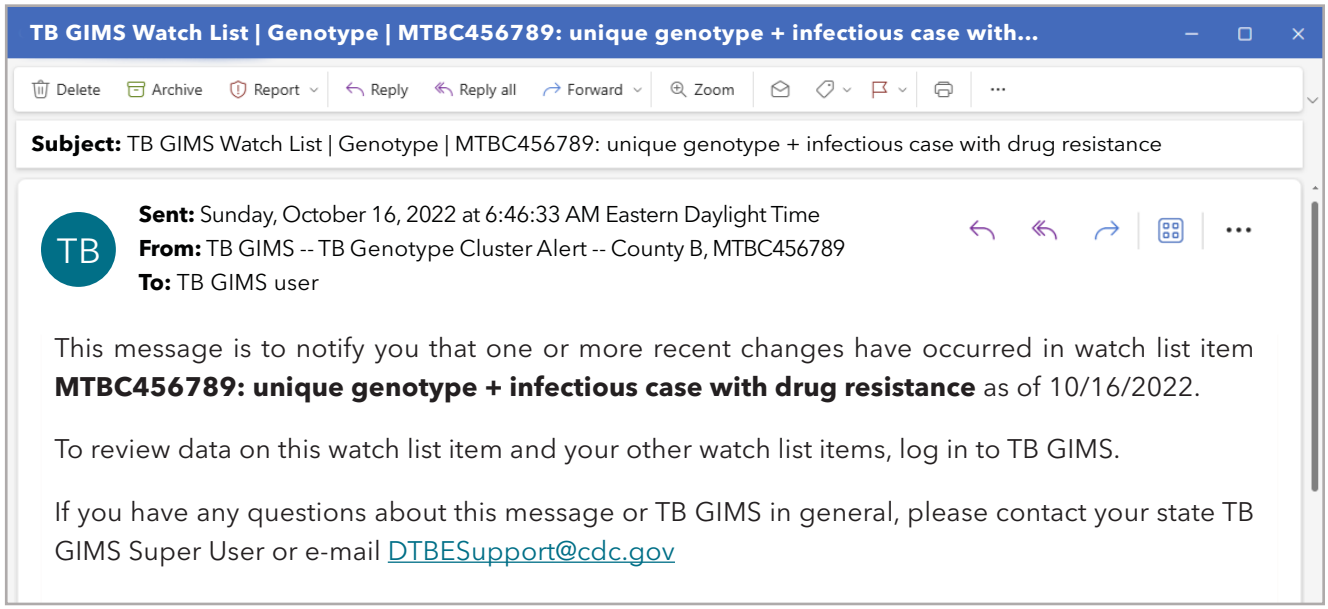
Key concepts from Example 2

- Assess a cluster based on available information (assessment without known epidemiological links),
- Develop action items during review meeting (for example, staff member tasked to generate watch list item, review national distribution report quarterly), and
- Create a TB GIMS watch list to monitor a cluster for future activity.

Example 3: Reprioritization of a cluster to Priority 1 in County B

On October 16, 2022, County B TB Program staff received a TB GIMS watch list notification for wgMLSType MTBC456789 (Figure 6) that had been previously determined to warrant monitoring for additional cases (see Example 2 above).

FIGURE 6: Sample TB GIMS watch list notification of additional cases of wgMLSType MTBC456789 in County B



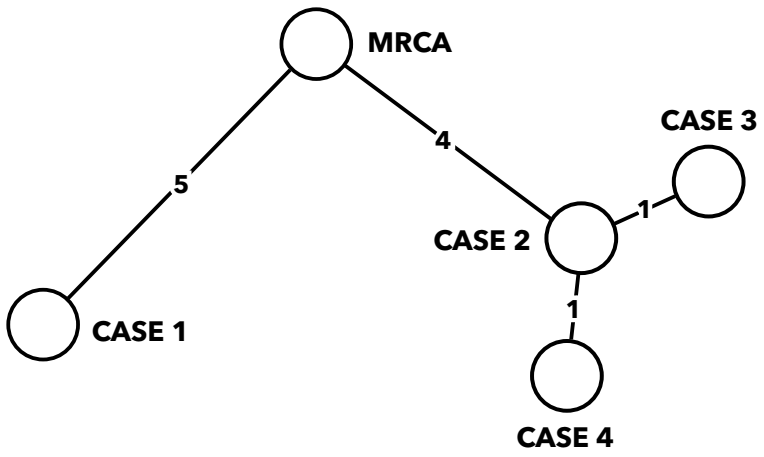
TB program staff reviewed cluster information in TB GIMS and determined that two additional cases with MTBC456789 had been identified. Now, there are four cases with a wgMLSType that is unique to County B in the past three years. TB program staff updated their previous line list to include the two new cases and re-assessed the cluster during their weekly cluster review meeting (Figure 7A).

FIGURE 7A: Updated line list of patient characteristics and TB risk factors, wgMLSType MTBC456789, County B

Case	Count Date	Sex	Age	Race/ Ethnicity	Origin of Birth	Pulmonary Disease	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless	Known Epi Link
Case 4	10/12/2022	F	63	Black	U.S.-born	**Yes**	**Positive**	**Yes**	**Isoniazid**	Negative	No	No	No	None
Case 3	10/10/2022	F	44	Asian	U.S.-born	No	Negative	No	**Isoniazid**	Negative	No	No	No	None
Case 2	7/18/2022	M	42	Hispanic	U.S.-born	Yes	Positive	No	**Isoniazid**	Negative	No	No	No	None
Case 1	2/8/2021	M	68	Hispanic	U.S.-born	No	Negative	No	**Isoniazid**	Negative	No	No	No	None

Upon re-review of the cluster, staff noted a lack of social risk factors. However, two new cases with isoniazid-resistant TB have been diagnosed within a month, of which one had infectious TB (pulmonary site of disease, sputum smear positive, and cavitary disease), and there were no known epidemiologic links between the patients. The increase in the number of cases in MTBC456789 in a 1-month period indicates there may have been recent transmission associated with this wgMLSType. As part of the follow-up, the team requested an updated wgSNP comparison. The updated results supported their suspicion of recent transmission among the three most recent cases (Figure 7B).

FIGURE 7B: Updated phylogenetic tree depicting genetic relatedness among isolates with MTBC456789



Based on this information, the team increased the priority of this cluster from Priority 2 to Priority 1. A Priority 1 classification had been previously determined to indicate active investigation of the cluster. Staff members were assigned responsibility for initiating a cluster investigation of all four patients involving 1) medical chart data abstractions, 2) social media searches, and 3) re-interviewing each patient with a questionnaire tailored to the cases in this cluster.

Through active investigation, program staff were able to identify additional contacts not previously screened during the initial contact investigations, possible sites of TB transmission at a church and a single-family home, and epidemiological links between cases through shared contacts and locations. By identifying and prioritizing genotype clusters, the local TB staff were able to focus valuable resources on interrupting TB transmission in their county.

Key concepts from Example 3

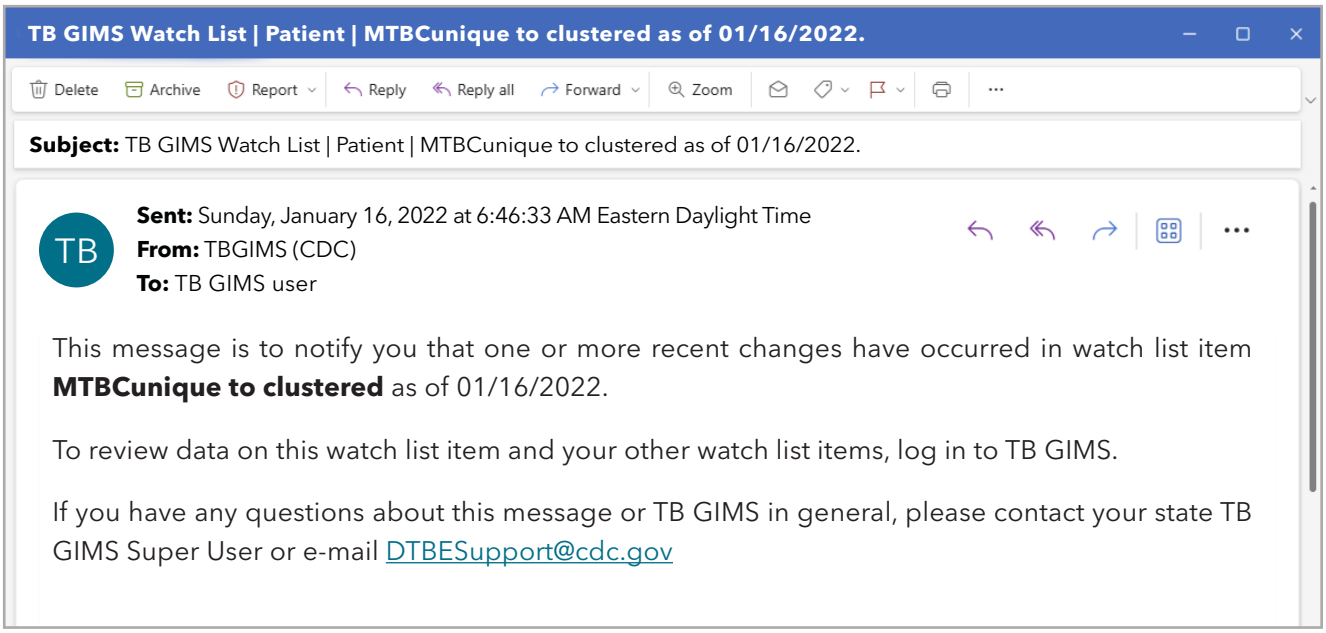
- Review a watch list item that generates a notification for recent activity related to a previously reviewed cluster,
- Request an updated wgSNP comparison and re-evaluate cluster prioritization,
- Identify patient characteristics consistent with recent transmission (genetically similar isolates by wgSNP comparison, sputum smear positivity),
- Identify drug resistance and patient infectiousness as patient characteristics that increase the level of concern for potential cluster growth,
- Illustrate how a program can use TB GIMS alerts to identify clusters that may represent undetected outbreaks, reassess and prioritize a cluster based on new cases, and describe potential public health actions when recent transmission is suspected.

Example 4: Assessment of a new genotype cluster in County C, a jurisdiction with TB incidence lower than the national average

County C has a population of approximately 225,000 people and typically reports about five TB cases per year. In 2021, the county reported seven TB cases, corresponding to 2.2 cases per 100,000 persons, which was lower than the national average.

Due to the low incidence of TB in County C, staff had previously decided to review all newly clustered cases in their jurisdiction. One way that staff monitor for new TB clusters is by utilizing the TB GIMS watch list functionality, which can be set up to notify TB GIMS users anytime a wgMLSType in their jurisdiction changes from MTBCunique to clustered (Appendix Figure 5). On January 12, 2022, County C received a TB GIMS watch list notification that at least one case in their jurisdiction had a wgMLSType change from MTBCunique to clustered (Figure 8A).

FIGURE 8A: Sample TB GIMS watch list notification of MTBCunique to Clustered, County C



During the regularly scheduled cluster review meeting, staff determined this watch list alert was generated because one of their 2021 cases that previously had a unique genotype (MTBCunique) was recently updated to MTBC654321 due to the addition of a 2022 case. Reviewing data in TB GIMS, the cluster team noticed both cases were in patients who were U.S.-born white males in the same age group with a history of substance use (Figure 8B). One of the cases had clinical characteristics consistent with highly infectious TB (positive sputum smears and cavitary lesions).

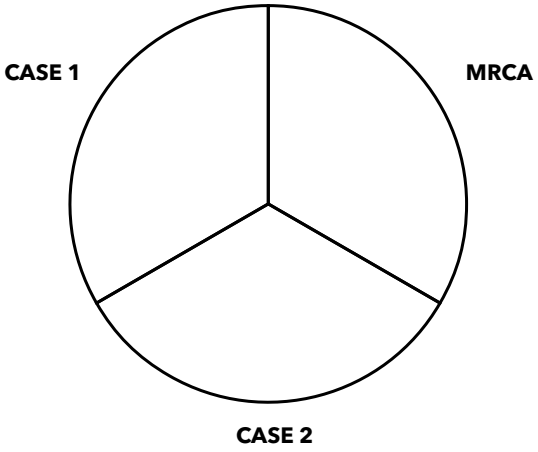
FIGURE 8B: Line list of patient characteristics and TB risk factors, wgMLSType MTBC654321, County C

Case	Count Date	Sex	Age	Race/ Ethnicity	Origin of Birth	Pulmonary Disease	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless	Known Epi Link
Case 2	1/9/2022	M	42	White	U.S.-born	Yes	Positive	Yes	None	Negative	Yes	No	No	None
Case 1	11/17/2021	M	36	White	U.S.-born	Yes	Negative	No	None	Negative	Yes	No	No	None

A staff member requested wgSNP comparison, where the isolates were determined to be 0 SNPs apart (Figure 8C).

FIGURE 8C: Phylogenetic tree depicting genetic relatedness among isolates with MTBC654321

Based on this prioritization scheme and the finding of the isolates being 0 SNPs apart, a public health staff member was assigned responsibility for 1) reviewing the contact investigations of each case for completeness and possible epidemiological links, and 2) re-interviewing each patient with a specific cluster investigation questionnaire. These active investigation activities allow County C to quickly identify and prevent TB transmission in their jurisdiction.



Key concepts from Example 4

- Review a TB GIMS watch list alert for cases that have changed from a unique to clustered genotype,
- Understand how a low-incidence jurisdiction may choose to assess and investigate a genotype cluster, and
- Utilize a pre-defined cluster prioritization system during the review process (for example, investigation warranted, investigation not warranted).

Appendix

Appendix A: Key Terms

Clinical TB cases

A clinical TB case is defined by meeting all of the following criteria:

- A positive tuberculin skin test result or positive interferon-gamma release assay for *M. tuberculosis*;
- Other signs and symptoms compatible with TB (such as, abnormal chest radiograph, abnormal chest computerized tomography scan or other chest imaging study, or clinical evidence of current disease);
- Treatment with two or more anti-TB medications; and
- A completed diagnostic evaluation.

False-positive TB culture (sometimes called "false-positive laboratory results")

Persons can be misdiagnosed with TB as a result of specimen mislabeling or cross contamination during specimen collection or during processing in the laboratory. Alternatively, a patient may in fact have TB, but cross contamination from another TB isolate results in an incorrect genotyping result. Additional resources for identifying and investigating false-positive results are available in the False-Positive Investigation Toolkit.

wgMLSType

Whole-genome multilocus sequencing typing (wgMLST) is a genotyping scheme that uses whole-genome sequencing (WGS) data. The wgMLST scheme for TB includes 2,690 different genetic loci, each of which is an individual gene in the genome. Isolates that match at ≥99.7% of the loci will form a genotype cluster, designated with a wgMLSType name (formatted as MTBC followed by a 6-digit number). Isolates that are <99.7% identical to any other isolate are designated as MTBCunique.

wgSNP comparison

Whole-genome single nucleotide polymorphism (wgSNP) comparison uses WGS data to identify single nucleotide polymorphisms (SNPs) that distinguish isolates in a genotype-matched cluster. SNPs result from mutations at a single position in the DNA sequence. The SNPs identified in a wgSNP comparison can be mapped on to a phylogenetic tree to diagram the genetic relationship among isolates. The number of SNPs that differ between isolates can be used in combination with available epidemiologic and clinical data to help assess whether TB cases are related by recent transmission.

Log Likelihood Ratio (LLR)

In TB GIMS, a measure of the geographic concentration over time of a local genotype cluster compared with the national average. The local area for the LLR calculation is defined by county boundaries and the time period is defined as the preceding 3 years.

Recent transmission

Recent transmission of *Mycobacterium tuberculosis* is typically defined as transmission occurring in the 2-3 years prior to diagnosis of the given case.

SaTScan

This software program analyzes spatial (and/or temporal) data using a scan statistic to detect geographically defined disease clusters and evaluate the statistical significance of each cluster. Significant localized concentrations of cases are detected by zip code location rather than by county or state borders.

TB GIMS

The TB Genotyping Information Management System (TB GIMS) is a secure web-based system that facilitates the linking of genotyping results with patient data reported to the National Tuberculosis Surveillance System, allowing users to review and analyze data related to TB genotype clusters. For questions about access to TB GIMS, contact TB GIMS staff by email at DTBESupport@cdc.gov.

TB GIMS Alerts

Cluster detection alerts are generated using two methods in TB GIMS:

1. LLR Alert
   LLR alerts are based on a county-level log-likelihood ratio (LLR) statistic (see LLR above). LLR calculations are performed each week and cluster alerts are generated if the LLR statistic crosses a set threshold (such as, "None" to "Medium") and the number of cases increases (such as, 2 to 3 cases) from one week to the next. Clusters of 2 cases will only generate an alert if the count dates are within 1 year of each other.

   Categories for the alert level:

   - High alert, LLR ≥10
   - Medium alert, LLR 4–<10
   - No alert, LLR <4

2. Case Count Alert
   Case count alerts are generated if the count of genotype-matched cases within a county during a 3-year window increases from <3 cases to ≥3 cases from one week to the next.

Alerts are sent automatically by email to registered TB GIMS users who have requested these alerts.

TB GIMS Watch List

A watch list is a user-defined search established in TB GIMS for a specific genotype and jurisdiction that will flag and notify the user of recent activity when an additional isolate or linked patient record is added for the defined genotype.

Single Nucleotide Polymorphism (SNP)

A mutation at a single position (A, T, C, or G) in the DNA sequence. SNPs are identified through wgSNP comparisons of WGS data and are mapped onto a phylogenetic tree to diagram the genetic relationship among isolates.

Appendix B: How do TB contact investigations differ from genotype cluster investigations and outbreak investigations?

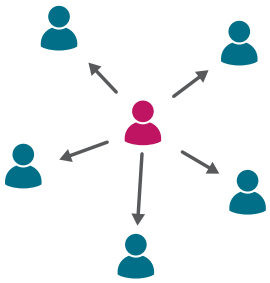
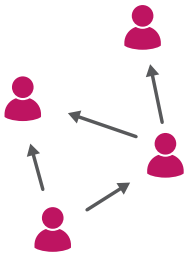
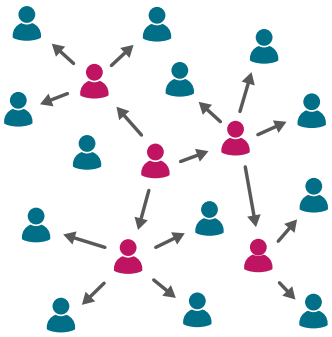
Contact investigations, genotype cluster investigations, and outbreak investigations are important activities in TB control. The ultimate goals of these investigations are similar—to identify, evaluate, and treat active TB cases and their contacts in order to interrupt transmission and prevent additional TB cases. In each investigation, understanding infectious periods for active TB cases is critical for determining where and when transmission may have occurred. Appendix Table 1 describes some key differences between each type of investigation.

Because outbreak investigations assess the overall potential for ongoing transmission of *M. tuberculosis*, outbreak investigations encompass contact and cluster investigation activities that may already be in progress. Findings from contact investigations and cluster investigations are often the earliest indications of an outbreak. For example, a contact investigation may identify ongoing transmission when numerous contacts have active TB disease. Similarly, a cluster investigation may identify new epidemiologic links between cases, leading to the identification of more recent transmission than had been previously noted.

It is important to note that not all matching genotype results represent recent transmission. A successful investigation of cases and contacts, however, allows state and local TB programs to promptly identify recent transmission and implement appropriate interventions.

Additional information on contact investigations and calculating infectious periods,[10,11] cluster investigations,[12] and outbreak investigations[9] is available from the Centers for Disease Control and Prevention.

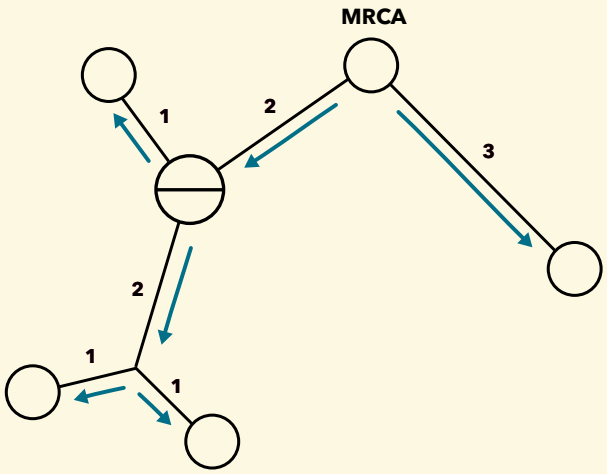
APPENDIX TABLE 1: Relationship between TB Contact Investigations, Clusters Investigations, and Outbreak Investigations

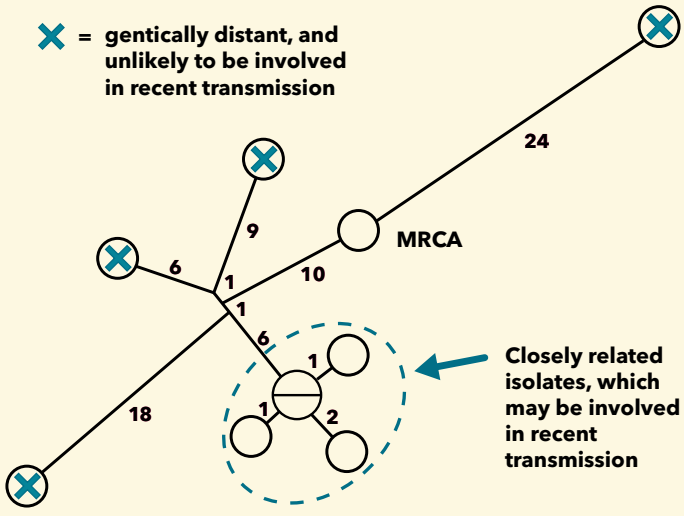
	TB Contact Investigation	Genotype Cluster Investigation	Outbreak Investigation
TB investigations are overlapping activities that should be utilized as needed to prevent and interrupt TB transmission.			
Case =  Contact = 			
Focus	Identify and treat TB infection and active disease among contacts of a single patient recently diagnosed with TB.	Identify recent transmission by considering possible relationships among TB cases that are genotypically matched.	Identify and prioritize the contacts of the outbreak patients so that they can be promptly and appropriately evaluated and treated.
Emphasis	Use information about a single TB case to identify, evaluate, and treat contacts of that case who may have been exposed during the patient's infectious period; this is a routine part of TB control.	Identify epidemiological links to help determine where, when, and by whom recent TB cases may have been infected.	Identify the most likely source case(s) and implement interventions that interrupt ongoing transmission.
Time frame of interest	Contacts are defined based on the patient's infectious period.	While genotype clusters in some jurisdictions can extend back over many years, cluster investigations typically focus on cases diagnosed in the last 2–3 years in a defined geographic area.	Outbreak investigations typically focuses on cases diagnosed in the last 2–3 years in a defined geographic area and an indistinguishable outbreak genotype.
Personnel involved	Local public health staff, including the TB program manager, nurse case managers, and field-based staff.	In addition to staff who routinely conduct contact investigations, cluster investigations may also include local staff such as epidemiologists, or other TB professionals such as TB controllers, TB genotype coordinators, laboratorians, and other state TB programs.	Because an outbreak indicates that there is potential for extensive recent transmission, an outbreak investigation should always be considered a public health emergency and involve combined efforts from multiple individuals and organizations, both within and outside the health department.

Appendix C: Guide to interpreting a phylogenetic tree for investigation of recent TB transmission

- Based on CDC's general experiences using wgSNP analysis for investigating recent transmission:
  - Isolates with 0–5 SNP differences are considered closely related
  - Isolates with 6 or more SNP differences are considered genetically distant
  - SNP thresholds will vary depending on the methods used for the wgSNP analysis, and cannot be compared to thresholds used by other groups with different analysis methods
  - These recommended SNP thresholds may change as CDC's wgSNP analysis methods are further developed or based on results of a formal validation analysis of SNP thresholds
- Whole-genome sequencing data should always be reviewed in context with available clinical and epidemiologic data

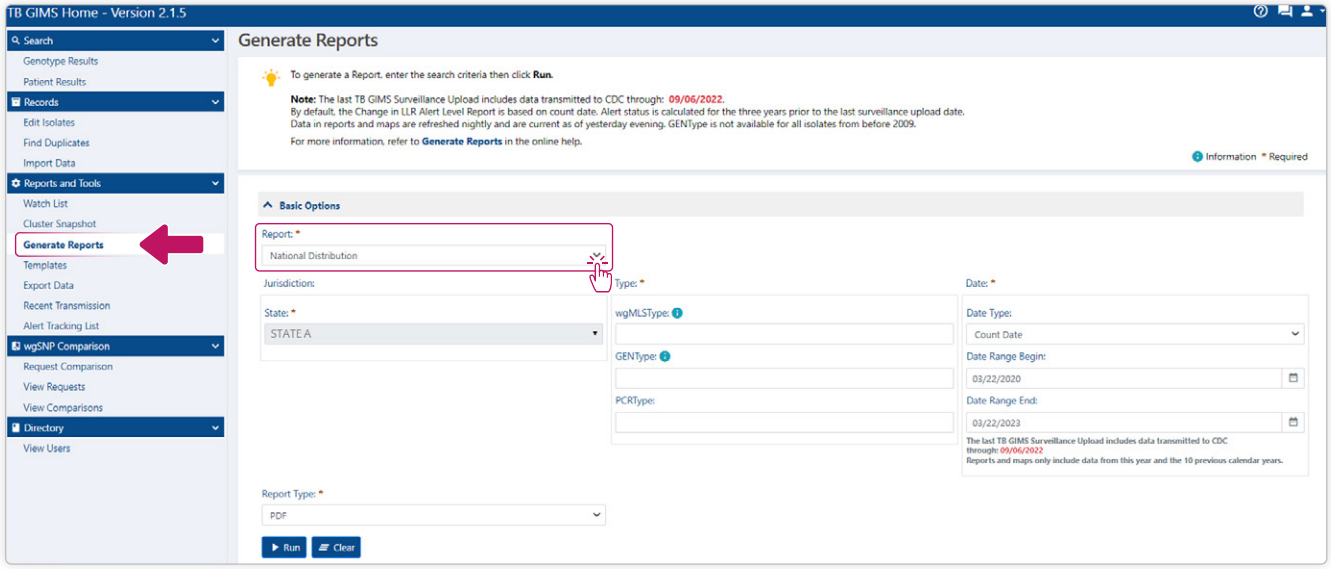
- Isolates are shown as circles (called nodes) and are labeled with the isolate accession number
- Isolates with the same genome type (meaning the same sequence) are displayed together in one node
- Nodes are connected by lines proportional in length to the number of SNPs that differ between the isolates
  - The lines are labeled with the number of SNPs
  - MRCA = Most Recent Common Ancestor
  - MRCA is a hypothetical genome type (not an actual isolate) from which all isolates on the tree are descended and serves as a reference point for examining the direction of genetic change

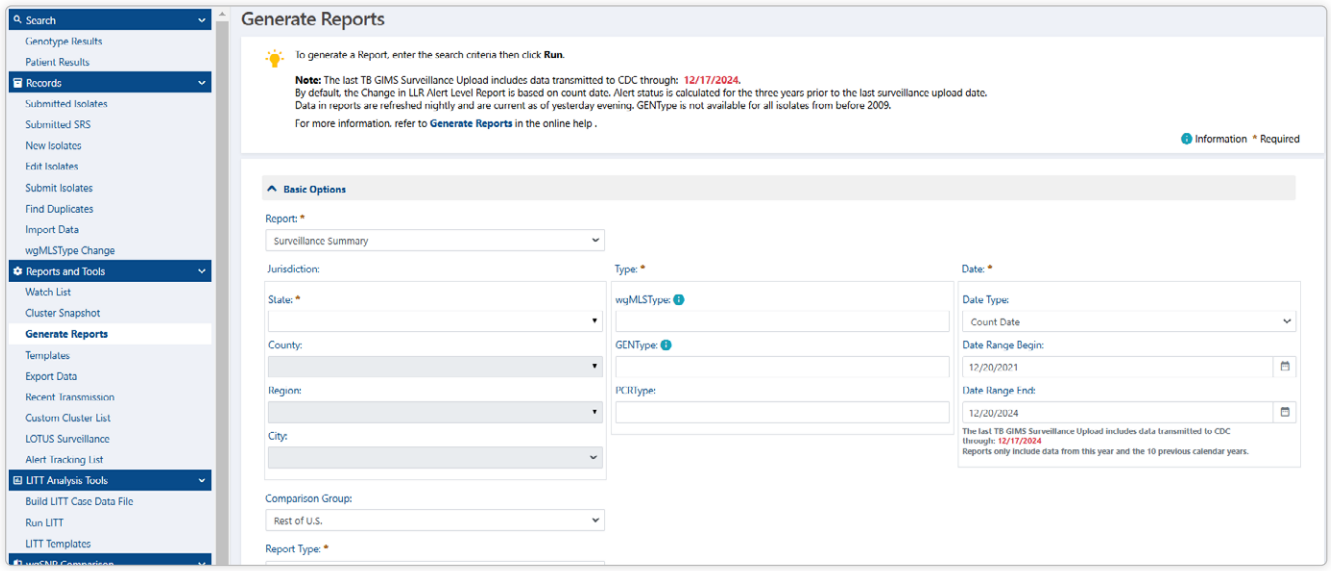




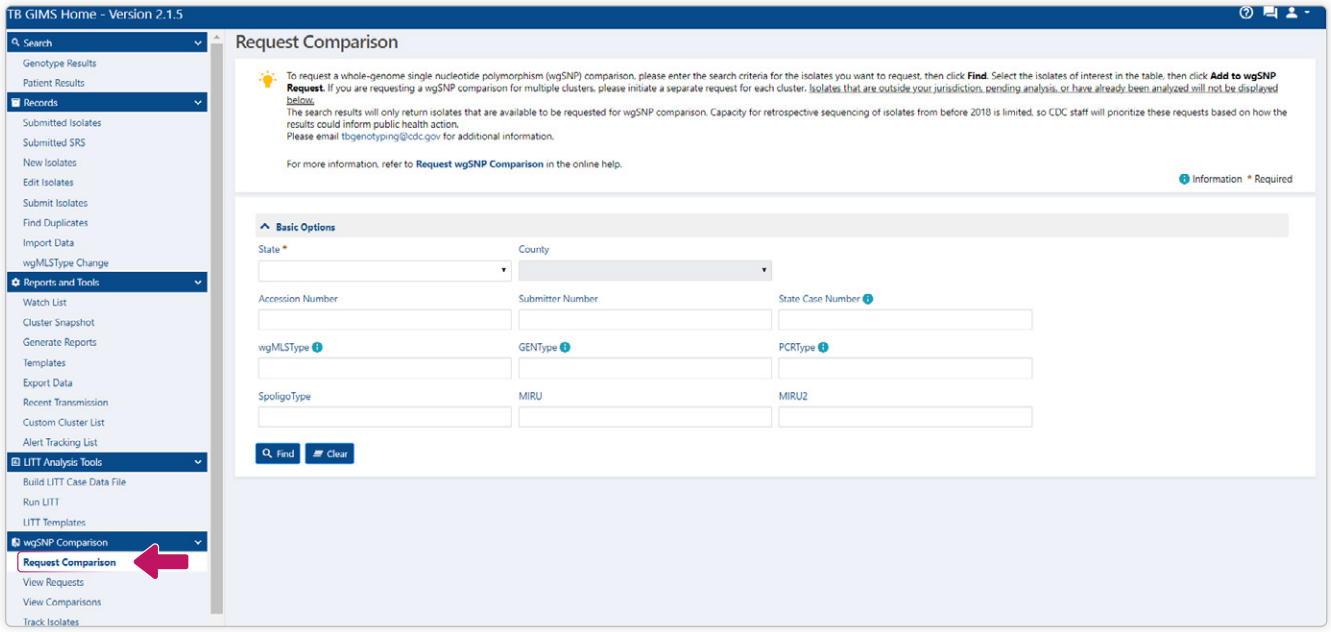
Appendix D: Resources for Navigating TB GIMS

APPENDIX FIGURE 1: Creating National Distribution and Surveillance Summary Reports of a wgMLSType in TB GIMS

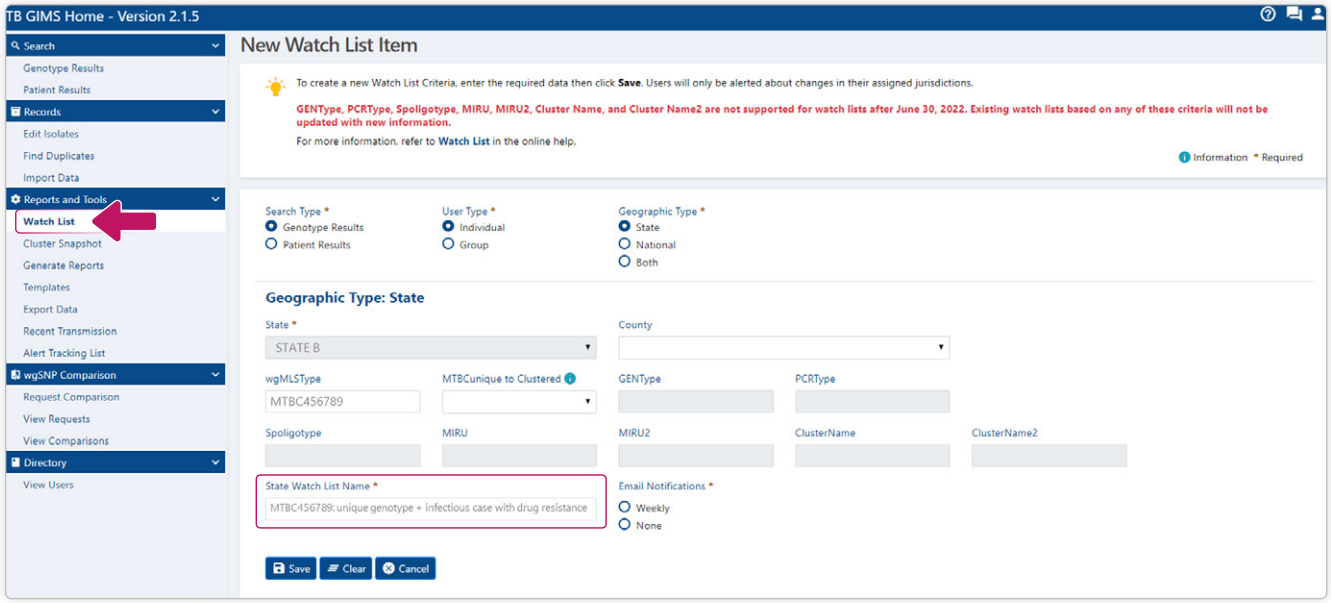




APPENDIX FIGURE 2: Requesting wgSNP comparison in TB GIMS

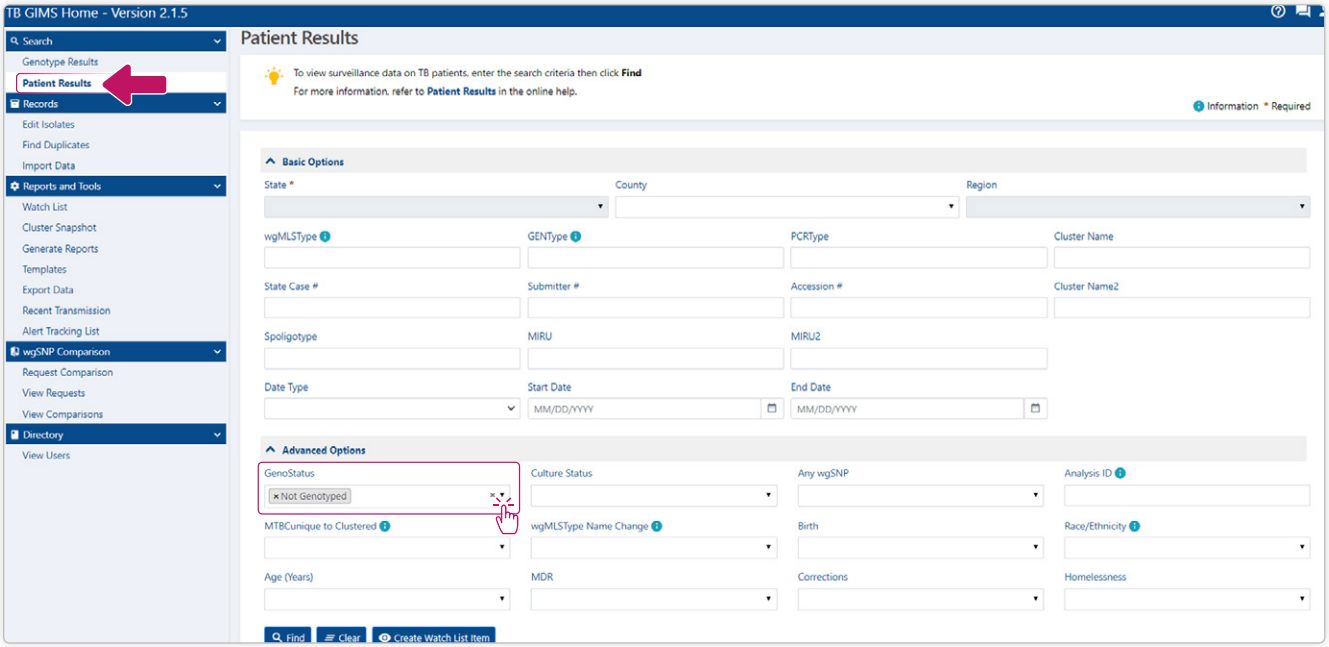


APPENDIX FIGURE 3: Creating a watch list in TB GIMS to monitor for additional cases in a specified genotype



The TB GIMS view shown may differ based on user role and jurisdiction.

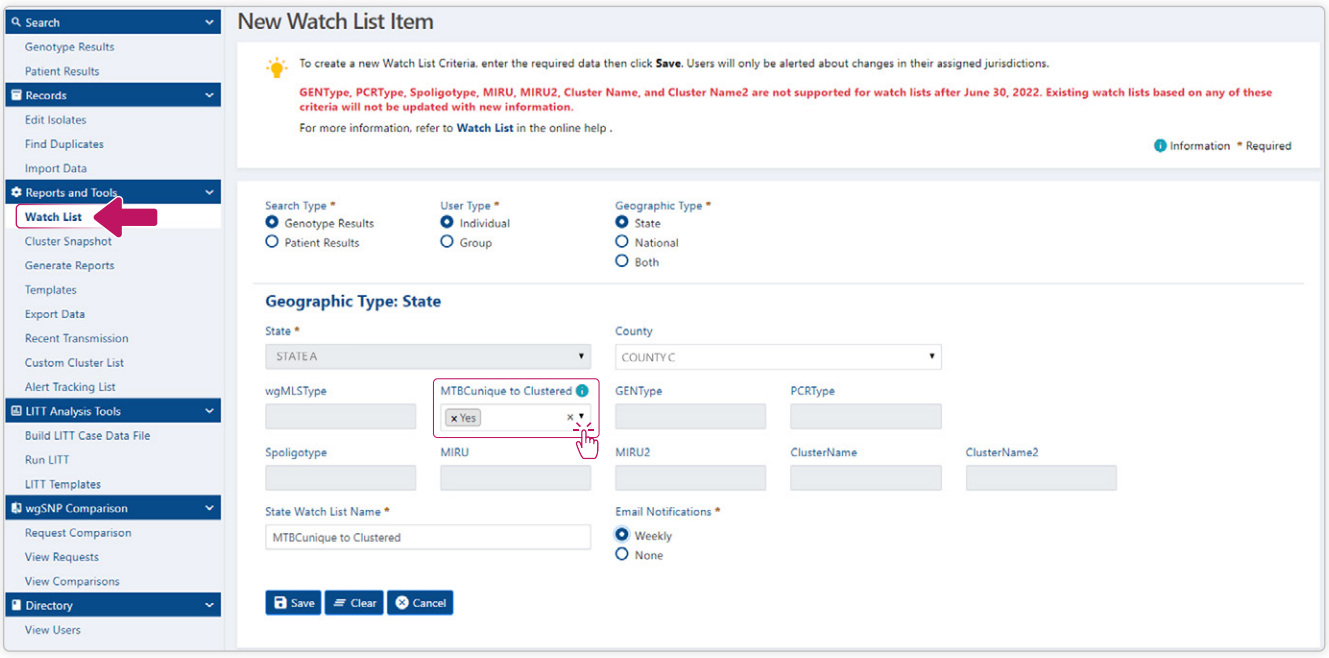
APPENDIX FIGURE 4: Querying clinical or non-genotyped TB cases in TB GIMS



The TB GIMS view shown may differ based on user role and jurisdiction.

To view cases without genotype results in TB GIMS, users can select "Not Genotyped" under "Advanced Options" in patient results. TB programs may also consult local TB surveillance databases to review clinical and non-genotyped cases that may be related to a genotype cluster of concern.

APPENDIX FIGURE 5: Creating a watch list in TB GIMS to monitor for when a genotype changes from unique to clustered



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